Control of Retinal Sensitivity

II. *Lateral Interactions at the Outer Plexiform Layer*

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ABSTRACT Test stimuli, presented at the center of the bipolar cell receptive field, spanning less than 2 log units of intensity, elicit the full range of graded response. The intensity range of test stimuli that elicits the graded response depends upon the background conditions. A higher range of log test intensities is required to elicit the graded bipolar response in the presence of surround backgrounds. But surround backgrounds can also serve to unsaturate the bipolar response and thereby increase sensitivity under certain conditions. The results suggest that a second stage of sensitivity-control is mediated by the horizontal cell system at the outer plexiform layer, concatenated with the effects of adaptation in the photoreceptors.

INTRODUCTION

In an accompanying paper (Normann and Werblin, 1974) we showed that steady background illumination affected the intensity-response relation for both rods and cones and controlled their sensitivity so that the rods became saturated, but the response range for the cones, although limited to about 3 log units, always encompassed the background intensities. The receptor activity is carried by antagonistic pathways that are concentrically organized at the outer plexiform layer to form the bipolar cell receptive field. These antagonistic interactions mediate a second stage of sensitivity control.

The bipolar cell response can apparently be modified by either surround or full field backgrounds. Werblin and Dowling (1969, Fig. 8) showed that surround backgrounds could alter the range of intensities over which the bipolar cell center response was graded. Werblin (1971) showed that full field backgrounds could serve to realign the intensity range over which the response of horizontal and bipolar cells generated a graded response to diffuse stimuli, but he failed to distinguish between the effects of center and surround. This is an important distinction because alterations in the bipolar response could reflect

changes in receptor activity, or result from lateral interactions at the outer plexiform layer, or both.

Lateral interactions forming the surround of the bipolar cell receptive field are presumably mediated by the horizontal cell system with processes that extend from the surround to the center of the bipolar receptive field. Maksimova (1969) and Naka and Witkovsky (1972) have shown that the effects of an antagonistic surround at the ganglion cell level can be duplicated in fish when horizontal cells are artificially hyperpolarized by currents passed through an intracellular electrode. Baylor et al. (1971) artificially hyperpolarized horizontal cells in turtle and showed a depolarizing effect in photoreceptors. These results support the hypothesis that horizontal cells mediate at least one form of lateral antagonism (Werblin and Dowling, 1969) and suggest further that lateral antagonism is carried through a feedback (recurrent) pathway.

Psychophysical experiments suggest a sensitizing role for surround backgrounds. Crawford (1940) and Ratoosh and Graham (1951) showed that threshold for a test flash centered upon a background disk was reduced as the disk expanded to encompass more of the surround. Westheimer (1965) used a separate annular background and showed that he could sensitize the center of a test field where threshold had been elevated by a background disk.

These results suggest that surround backgrounds can sensitize or desensitize the visual system. Since bipolar activity is modified by surround backgrounds, the outer plexiform layer is a potential site mediating these sensitivity changes. By recording intracellularly from the bipolar cells in *Necturus* I have studied the effect of surround backgrounds on the response characteristics of the bipolar center. The results show how the relationship between receptor and bipolar activity is modified by the antagonistic surround, and suggest a role for the surround in either sensitizing or desensitizing the center of the bipolar receptive field.

METHODS

Preparation

As in previous experiments (Werblin and Dowling, 1969; Werblin, 1971) mudpuppies were stored at about 10°C in a tank. They were decapitated and the anterior of one eye was carefully dissected away using a lab-built infrared dissection microscope. The vitreous in mudpuppies is fairly liquid; it is drawn out of the eyecup with a capillary tube 0.5-mm inside diameter. The entire head was mounted in a special chamber and positioned so that the eye could be stimulated optically and a micropipette could be inserted into the retina. This preparation was useful, judging from the constancy of the electroretinogram, for about 4 h.

Electrodes

Pyrex capillary tubing, Corning no. 7740, 1 mm OD, 0.5-mm ID (Corning Glass Works, Corning, N. Y.) was drawn down to a fine (less than 0.1-μm) tip with a Liv-

ingston-type microelectrode puller (Otto Hebel, Rutledge, Pa.). The pipettes, having been previously filled with strands of fiberglass, were filled with a no. 30 pediatric lumbar puncture needle. 3–5 M potassium acetate gave less noisy recordings than filling with 3 M potassium chloride or other alternatives. The pipettes were lowered into the retina using a homemade hydraulic system consisting of hypodermic syringes mounted back-to-back through Teflon tubing. The hydraulic system is necessary to isolate the experimenter mechanically from the electrode and the preparation, as the slightest vibration tends to dislodge the electrode from the cell being studied.

Stimulator

Two Tektronix 604 display oscilloscopes with special P11 phosphors were used as the stimulators (Tektronix, Inc., Beaverton, Ore.). Special patterns, consisting of spots, rings, disks, and windmills can be generated electronically and displayed on these oscilloscopes. The advantage of this stimulus system is that a variety of patterns can be flashed or varied continuously in intensity, position, or size. The disadvantage of the system lies in the limited intensity range available for stimulation and in the fact that the images tend to "bloom" when the intensity is increased by more than about 4 log units above threshold. For the present experiments, the limited intensity range, covering about 4 log units above threshold for most retinal cells, was quite adequate.

The intensity of each oscilloscope was monitored by a photomultiplier, then fed to a logarithmic amplifier, and finally displayed along with the recordings on a storage oscilloscope. The two images, one from each scope were combined with a half-silvered mirror, then optically reduced and focussed upon the retina.

For some of the bipolar cell experiments a signal proportional to the log stimulus intensity at the center of the bipolar field was fed directly to the x-axis of the oscilloscope. The y axis was driven by a signal proportional to the cell response, so an intensity-response curve was generated directly on the face of the oscilloscope. This facilitated rapid evaluation of the characteristics of the bipolar cell operating curve for a variety of stimulus conditions.

In other experiments the stimulus consisted of an average intensity level, presented to the center of the bipolar receptive field, and modulated with a square wave. This stimulus was accomplished by driving the z axis of the display oscilloscope with a function generator that produced a square wave superimposed upon a steady DC level. The intensity of the stimulus was monitored as described above.

The experiments shown in Figs. 1 and 2 were performed with diffuse stimuli covering a broader range of background and flash intensities than was possible with the CRT displays. The stimulator used in these experiments was similar to that described in the accompanying paper by Normann and Werblin (1974). Briefly, it consisted of a pair of light sources with intensities modified by neutral density filters converging through light pipes upon the retina. The source used as background was presented for 8 s; the "test flash" from the other source was substituted for background for 1 s during each stimulus cycle. Intensities are calibrated with those of the previous paper.

Taping and Photographing

The data from the recording electrode, two photomultipliers, and voice were recorded on a Vetter, model A, (A. R. Vetter, Rebersberg, Pa.) eight-channel FM tape system

with bandwidth limited to 1,000 Hz. Later, the signals were played back onto a Tektronix model 5000 series storage oscilloscope and photographed with Polaroid film (Polaroid Corp., Cambridge, Mass.) from the stored image. In order to form a black line-on-white background reproduction, the Polaroid pictures were photographed using Kodak type 2575 high contrast direct positive film (Eastman Kodak Co., Rochester, N. Y.) which has a negative "gamma" and therefore produces a direct positive transparency. This transparency was then used as the "negative" to make prints that were reversed from the original Polaroid photographs.

RESULTS

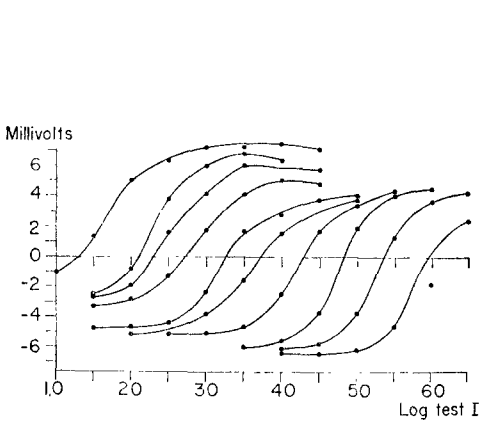
Identification of Cells and Background Conditions

Other studies (Werblin and Dowling, 1969; Werblin, 1970 and 1971; Kaneko, 1970; Matsumoto and Naka, 1972) have shown that the depolarizing and hyperpolarizing bipolar cells have many common properties in a variety of vertebrates. The receptive fields are concentrically organized with centers ranging from 300 to 500 μm in diameter in mudpuppy, but the antagonistic surround extends over broader retinal regions. Turtle cones also appear to have concentric antagonistic receptive fields (Baylor et al., 1971; Cervetto and MacNichol, 1972), but in mudpuppy the antagonistic effect of the surround measured in cones is minimal (Normann and Werblin, 1974 and unpublished observations). Therefore, in mudpuppy the bipolars can be distinguished from the cones by three criteria: (*a*) longer latency of response (Normann and Werblin, 1974), (*b*) dramatic antagonistic (versus minimal) surround effect, and (*c*) broader receptive field centers (Werblin, 1970). I have used results from studies of the depolarizing and hyperpolarizing bipolars interchangeably, presenting the best data from experiments on either type. Each experiment here is meant to represent the behavior of both types of bipolar.

These experiments are primarily concerned with the effects of surround antagonism, and no attempt was made to measure spectral sensitivity. However, all of the effects described here have been observed in different cells under both scotopic and photopic conditions, so the phenomena are not clearly associated with either rod or cone activity. In this paper I have taken the background level of 3.5 log units as the transition point from scotopic to photopic conditions (Normann and Werblin, 1974). The backgrounds used in these experiments cover a range extending from absolute threshold to about 2.5 log units into the photopic range as measured in the rods and cones (Normann and Werblin, 1974), and the curves in these figures are similarly calibrated in intensity.

Response to Diffuse Flashes at Different Full Field Backgrounds

Figs. 1 and 2 show the intensity-response curves for a horizontal and bipolar cell under stimulus and background conditions similar to those used in the previous paper. Similar experiments in horizontal cells have been reported by



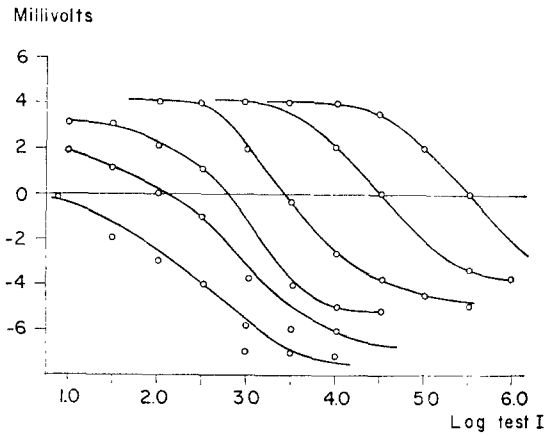


FIGURE 1 FIGURE 2

FIGURE 1. Intensity-response curves for the horizontal cell elicited by full field test flashes substituted for background. The curves become negative to the right because the horizontal cells hyperpolarize with increasing intensity. Responses to test intensities above background are plotted below the zero line; responses to test intensities above background are plotted above. The background intensity for each curve is given by the intersection of the curve with the zero line. This is the intensity of the substituted test flash that elicited no response. The left-most curve is the response curve in the presence of lowest background. The intensity scale is the same as that used in the previous paper. Peak level was measured with respect to membrane potential just prior to the response. Curves are drawn by eye through the experimentally derived points.

FIGURE 2. Intensity-response curves for a depolarizing bipolar cell elicited by full field flashes. These curves are plotted from the peaks of bipolar response to substituted test flashes, above and below background. The background intensity for all curves is given by the intersection of the curves with the zero line; this is the intensity of the substituted flash that elicited no response. Peak responses are plotted, measured from membrane potential just prior to response. Curves are drawn by eye.

Byzov and Kusnezova, (1971). 1-s test flashes were substituted for background every 8 s. The test flashes were presented in 0.5-log unit steps and in ordered sequence. The intracellular responses from the cells, at a few representative background levels are shown in Figs. 3 and 4; the peak magnitudes of these responses measured from the base line just preceding the response, were plotted in Figs. 1 and 2. At background levels near absolute threshold the intensity-response curves for both horizontal cells and bipolars are relatively shallow and most of the response range lies at intensities above the background level, as shown previously for the rods. As background is raised, the slope of the curves increases gradually and the response range becomes equally divided between test flash intensities above and below the background level, as shown previously for the cones (Normann and Werblin, 1974).

A measure of the slope and range of the curves is obtained by aligning them with the relation

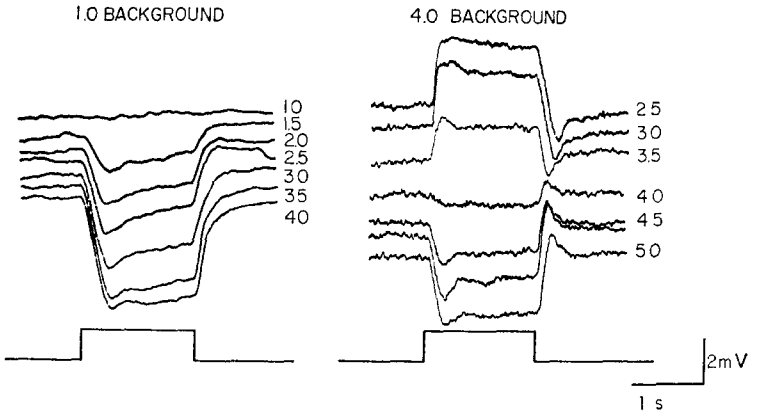


FIGURE 3. Time-course of response in horizontal cell to test flashes substituted for background. Left: in the presence of 1.0 background all responses are hyperpolarizing. Right: in the presence of a 4.0 background, test flashes lower than 4.0 elicited a depolarizing response. The 4.0 test flash elicited a slight hyperpolarization because it was not precisely calibrated with the 4.0 background channel.

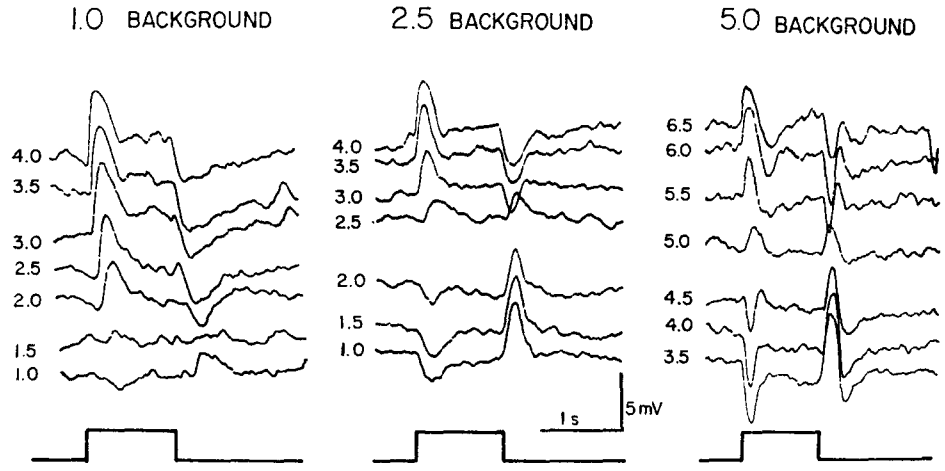


FIGURE 4. Time-course of response in a depolarizing bipolar cell. Test flashes were substituted at different backgrounds as in previous figure. The sustained phase of the response became smaller at higher backgrounds. The peaks of the response at *on* measured from the potential just prior to response were used to plot the intensity-response curves shown in Fig. 2.

$$V/V_{max} = I^n/(I^n + k^n),$$

where V is the response magnitude, V_{max} is the magnitude of maximum response used for normalization, I is the stimulus intensity, k is the value of I for which the expression has the value of one-half, and n is varied to fit the curves (Naka and Rushton, 1967, Naka, 1969). For flashes of comparable duration

(seconds), n has the value of 0.7 for the photoreceptors in the previous paper. For horizontal cells, n varies from about 0.7 at low backgrounds, where responses are evoked by increments, to 1.0 at the higher background levels, where responses to both increments and decrements are plotted. However, the value of n in the bipolars varies from about 1.0 at low backgrounds to 1.3 at higher background levels.

The variation in the value of n for cells postsynaptic to the photoreceptors, as a function of background level, could result from the separate inputs from rods and cones in the mesopic range as shown by Steinberg (1969) in the cat horizontal cells. The response curves for the two receptor populations are not aligned at low backgrounds so the combined output might span a wider range of intensities than spanned by either class of receptor alone. This appears to be the case for the mesopic PIII shown previously (Normann and Werblin, 1974). However, the curves might also be extended as a result of the stimulus procedure. Test flashes were presented every 8 s in order of increasing intensity, so each test flash could have reduced sensitivity for the subsequent flash. Even if this were the case, it is still striking that the value of n for the bipolars, when the peak value of the response is measured, is greater than that for either the horizontal cells or receptors.

Variation of DC Level with Background

Bipolar cell recordings were often stable enough that DC level was maintained to within 1 mV (about 10%) throughout the duration of a recording sequence. When the DC level was stable, the absolute maximum and minimum values of bipolar response potential remained fixed for all values of background illumination. From this it is possible to infer the DC level at background even in the less stable recordings. The magnitude of the maximum response to substituted test stimuli below background intensity is a measure of the difference between the DC level at that background, and the initial dark potential level.

Using the method of evaluating the DC level from the decremental response, the DC behavior at the bipolar cell shown in Figs. 2 and 4 as a function of background was plotted in Fig. 5, along with the peak response to test flashes at the 3.75-log background level. The DC level in the horizontal cell is also plotted by comparison as the dashed curve in the figure. Both curves seem to reflect the DC properties of the receptors. In the scotopic range, the DC level increases as background is increased, as shown for the rods and the initial portions of the cone curves. However, the DC level remains constant throughout the photopic range, as shown for the cone system (Normann and Werblin, 1974).

These results suggest that most of the adaptation that reduces the DC level as background increases is mediated at the receptor level as shown pre-

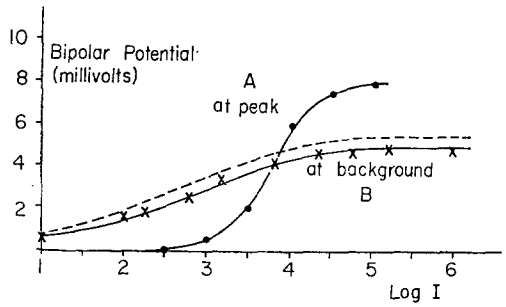


FIGURE 5. Intensity response curves for peak and plateau of bipolar response to diffuse flashes. The peak response curve was taken for the bipolar at a background of 3.75 log units. The solid background curve shows the steady bipolar potential at each background illuminance. The dashed curve shows the steady horizontal cell potential at each background level.

viously. An additional component is introduced at the receptor terminal through horizontal cell feedback. For example, compare the aspartate with the normal receptor responses in Normann and Werblin (1973). This horizontal cell effect is more clearly observed at the bipolar level, probably because bipolars are "downstream" from the interaction. The role of the horizontal cells in reducing the peak responses of the bipolars is evaluated below.

Extent of the Antagonistic Surround

There is good correlation between the magnitude of response in the horizontal cells and the diminution in response after the initial peak in the bipolars. In these experiments a test disk of constant intensity was expanded in diameter to cover more of the surround of the bipolar and horizontal cell receptive fields. By using a fixed intensity, a nearly constant stimulus was always presented at the center of the bipolar cell receptive field as the test disk was expanded. Therefore, the magnitude of the subsequent decrement in bipolar response, after the initial peak, due to the surround antagonism, was always measured against a constant center response. Fig. 6 shows the results of one such experiment. As the test disk was increased in diameter from ½ to 2 mm the horizontal cell response, and the decrement in bipolar cell response, following the initial peak both increased monotonically. However, the initial peak response in the bipolar recordings was relatively unaffected by the diameter of the test disk.

The magnitude of the antagonistic effect varied from cell to cell, but became consistently greater as background level was increased. For example, the bipolar in Fig. 6 A was antagonized by about 50% of its peak response magnitude by the surround. In Fig. 4, the bipolar was similarly antagonized by about 50% at the 1.0 background level, but by nearly 100% at the 5.0 background level.

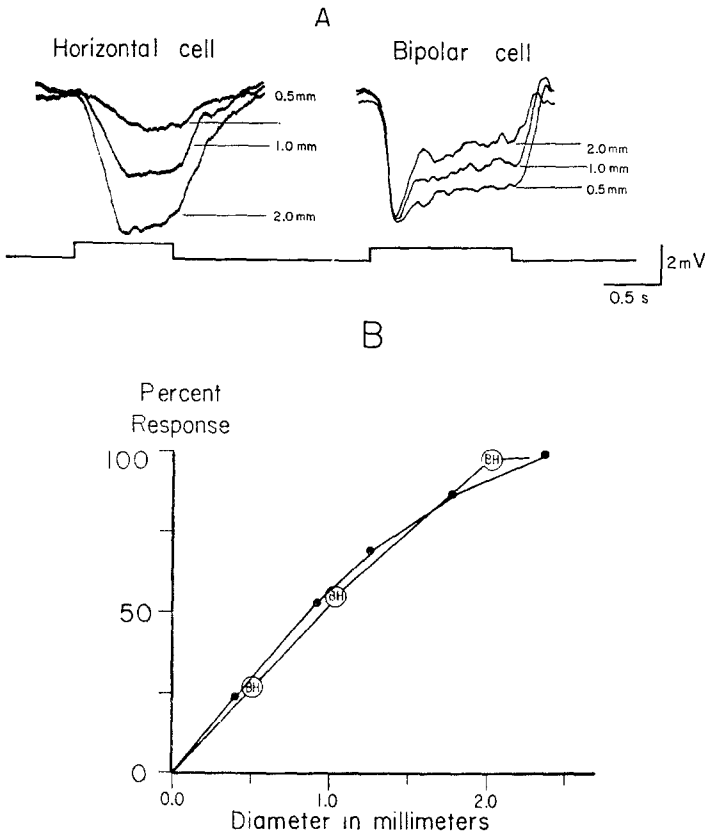


FIGURE 6. (A) Change in magnitude of response for different size test disks in horizontal cells and bipolars. For each cell the test disk of constant intensity but variable diameter, as indicated was centered on the receptive field of the cell. Larger disks elicited larger responses in the horizontal cell and larger antagonism of center response in the bipolar cell. (B) Plot of percent of maximum response in a typical horizontal cell and percent of maximum decrement of response in a typical hyperpolarizing bipolar cell (large circles), along with the predicted values of response weighted by the function $W(x) = Ae^{-4x}$ where x is distance from the center of the field in millimeters and A is an arbitrary constant (small circles).

To correlate the magnitudes of the decrement in bipolar response with the magnitude of the horizontal cell response at various test disk diameters, I used a test intensity that was not saturating for either cell, and then calculated the ratio of response at each disk diameter to the value at maximum diameter. Using these precautions, the level of activity in horizontal cells is well correlated with the magnitude of decrement in the bipolars for all test disk diameters over about 2 mm, as shown in Fig. 6 B. Beyond 2 mm the test disk often fell outside the retina of the mudpuppy.

The magnitude of the initial peak is not affected by the size of the test disk;

only the subsequent steady phase of response, which appears about 250 ms; after the peak is diminished for larger disks. This indicates that the magnitude of the initial peak elicited by a test flash of any diameter is a good measure of the central response. Therefore, the intensity-response curve shown in Fig. 2, where the magnitude of the initial peak in bipolar response to a *diffuse* flash was taken as a measure of activity, could be interpreted as the intensity-response curve for test stimuli presented at the bipolar cell center alone. To further confirm this, the center of the bipolar cell receptive field alone has been stimulated in the following experiments, and the intensity-response curves under these conditions are similar to those in Fig. 2.

It has been previously determined, both in tench (Naka and Rushton, 1967) and in mudpuppy (Werblin, 1970) that a spot stimulus, as it is moved further from the center of the receptive field for the horizontal cell, elicits a response that decreases according to the function

$$W(x) = Ae^{-4x},$$

where A is an arbitrary constant and x is measured in millimeters. It is probably fortuitous that the weighting function is similar in both these preparations since fish have quite different horizontal cell structures from mudpuppy (Dowling and Werblin, 1969; Stell, 1967). I have used the weighting function above to predict the magnitude of the horizontal cell response to flashing disks of increasing diameter, and the result is plotted along with the experimental curves in Fig. 6 B, showing a fairly good agreement. This suggests that the weighting of the bipolar cell surround, and the weighting of the horizontal cell response may both decrease with distance by a similar function, providing further evidence for the notion that the bipolar cells are embedded in a system of horizontal cells whose level of activity determines the level of lateral antagonistic input to the bipolars.

Effect of Lateral Antagonism on the Bipolar Intensity-Response Curves

Fig. 7 A illustrates a simple way to demonstrate lateral antagonism in the bipolar cell. The bipolar studied here was of the hyperpolarizing variety; steady illumination with a 300-μm spot at the center of its receptive field elicited a sustained hyperpolarizing response, (*a*). In the presence of this sustained center illumination, an annulus having an inside diameter of 500 μm and an outside diameter of 1 mm was flashed in the surround. (The results above indicate that an outside diameter of more than 1 mm would have been even more effective.) In the presence of the annulus, the centrally elicited hyperpolarization was reduced from level (*a*) to level (*b*).

Similar bipolar experiments have been performed by Kaneko (1970) in goldfish, and Matsumoto and Naka (1972) in frog. This approach generates

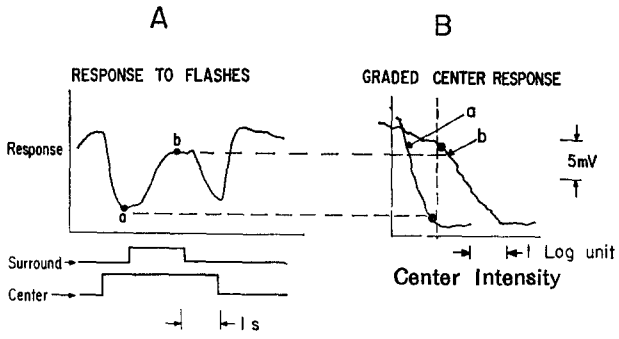


FIGURE 7. (A) Time-course of response of a hyperpolarizing bipolar cell to center flash reaching level *a* followed by the addition of a surround flash. The surround acts to antagonize the central response, so the initial hyperpolarization (*a*) is reduced and the membrane is driven back toward its initial dark level (*b*). (B) Intensity-response curves for the center of the bipolar cell receptive field with no background (*a*), then in the presence of a fixed intensity annulus (*b*) that shifted the response 1 log unit to the right. In this and following experiments, the annulus was 500 μm in inside diameter, 250 μm wide, and centered on the field. Central test spot was 300 μm in diameter. Its intensity, plotted along the abscissa, was varied gradually over a 3-log unit range in 6 s.

two potential levels for one pair of center and surround intensities, but there exist numerous combinations of center-surround intensities that generate the same or different potential levels (Werblin and Dowling, 1969, Fig. 9). In order to catalog a greater variety of center and surround intensities, the experiment shown in Fig. 7 B was performed. The intensity of the 300-μm central spot was continuously varied over a 3-log unit range at the rate of 0.5 log units/s, and its value was recorded along the abscissa of the graph. The response of the bipolar cell was recorded with values along the ordinate. In this way an intensity-response curve for the center of the bipolar receptive field could be plotted in just a few seconds. This procedure generated the curve marked *a* in the Fig. 7 B. The experiment was then repeated, but this time the center response was recorded in the presence of a surround background. The curve marked *b* was generated in this way; it is shifted to the right along the log intensity axis by about 1 log unit.

The response forms in Fig. 7A can be interpreted in terms of the curves in Fig. 7 B. With no surround present the central flash with intensity indicated by the dashed, vertical line, elicited a hyperpolarizing response indicated as *a* in both figures. Response *b* of less hyperpolarization was elicited in the presence of the surround and represents one point on the entire response curve that was shifted to the right.

The slope and range of each of the intensity-response curves shown in Fig. 7 B elicited by gradually increasing intensity at the center of the bipolar receptive field, in the presence of two levels of surround illumination, resemble the curves shown in Fig. 2 for full field illumination where the peaks of the

responses were taken for the points on the curves. The close relationship between the forms of the two curves, elicited under quite different conditions of stimulation, can be explained by the results shown in Fig. 6. There, the magnitude of the peak response to a test flash of any diameter is approximately the same as the magnitude of the sustained response to a small, centered flash of the same intensity. Therefore, the initial peak response to a diffuse flash is a good measure of the central response; the steady response decrement occurring after the initial peak appears to result from delayed surround antagonism.

The parallel shift in the bipolar curves in the presence of the surround, resembles the shift in receptor curves in the presence of background, (Normann and Werblin, 1974) but the shifting mechanism is quite different in this case. In the experiment of Fig. 7 the receptors at the center of the bipolar receptive field were not illuminated by the background surround that acted to shift these bipolar curves, so the receptor curves were probably fixed in position throughout the experiment. The signal that acted to shift the bipolar curve was probably carried by horizontal cell processes extending from the surround to the center of the field. If the surround background were to scatter into the center, a similar shifting of the bipolar curves, initiated at the *receptor* level might occur. The following experiment was designed to distinguish between the effects of center and surround backgrounds on the bipolar response curves, and helps to rule out scatter as a mechanism.

Different Effects of Center and Surround Backgrounds on the Bipolar Response Curves

In the following experiment I measured the bipolar cell response to the gradually increasing intensity of a central spot, in the presence of three different backgrounds: (*a*) an annulus, (*b*) a center background spot, (*c*) a broad background disk which represents the combined background spot and annulus.

Fig. 8 A shows the effect of the background annulus upon the bipolar operating curve. As in the preceding experiment, the curve was shifted roughly parallel to itself from left to right along the log-intensity axis when the background annulus was present. There was no significant change in the dark potential level of the cell in the presence of the annular background. Fig. 8 B shows the effect of the central spot background alone on the bipolar response curve. The bipolar cell was initially hyperpolarized by the central background spot to the level represented by the arrow (*b*), but the position of the remainder of the curve elicited by test intensities above that background was not greatly affected by the spot background; all activity still fell roughly along the original response curve. These two experiments serve to isolate the separate effects of center and surround backgrounds upon the operating characteristics of the bipolar cell: the central background like a small center test flash, simply hyperpolarizes the bipolar along the initial response curve; the

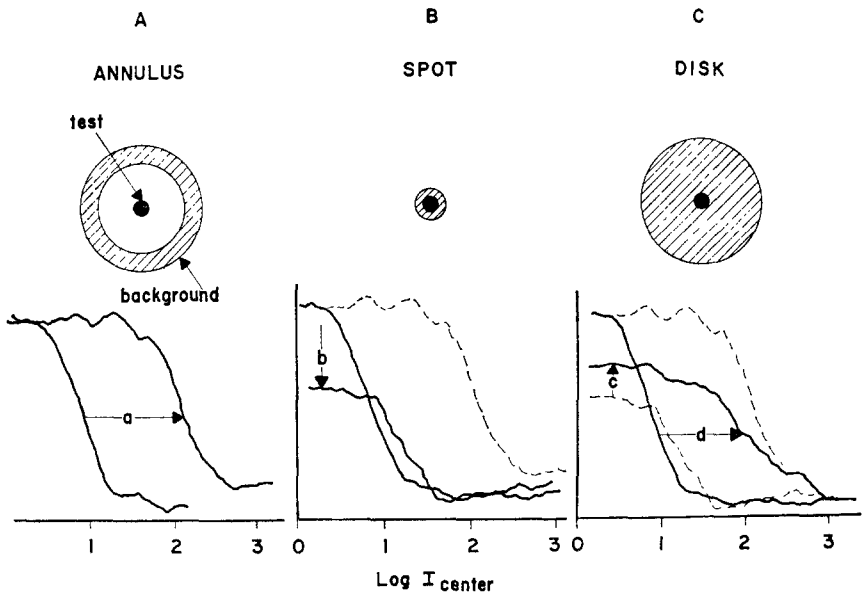


FIGURE 8. Combined effects of center and surround background on the form of the bipolar cell operating curves. (A) In the presence of a surround background the operating curve is shifted to the right, parallel to itself, as indicated by arrow *a*. (B) In the presence of a center background spot the bipolar cell is hyperpolarized along its original operating curve as represented by the arrow (*b*). (C) When the background spot is expanded to cover both the center and surround, the effect of the center background is antagonized (*c*), and the operating curve is shifted to the right (*d*). Solid circles represent the test stimulus at the center of the field, cross hatched regions represent the background conditions drawn approximately to scale, where the central spot is about 300 μm in diameter and the disk is about 500 μm in diameter. The total response range is about 10 mV.

surround background however, shifts the *position* of the operating curve without hyperpolarizing the cell.

The effects of both center and surround backgrounds, presented together in the form of a broad background disk are illustrated in Fig. 8 C. The central portion of the disk covered the center of the bipolar receptive field and served as a center background spot; the surrounding regions served as a surround background. The resulting response curve can be interpreted as follows. The bipolar cell was initially hyperpolarized by the center background (as in B), but this hyperpolarization was reduced by the presence of the surround (as in A). Therefore, the unit was less hyperpolarized initially by the broad disk than by the center spot (as in Fig. 6 A). In addition, the surrounding regions of the background disk acted to shift the response curve to the right along the intensity axis (as in A).

These results rule against scatter into the center of the field as a cause of the curve shifting, because even a spot of the same intensity as the annulur sur-

round (curves *b*) has less of a shifting effect than the surround itself (curves *a*) The experiment was performed under scotopic conditions, where the response curves for the rods at the center of the bipolar receptive field, illuminated by the background spot, would not be greatly shifted by the background. However, similar results were obtained under photopic conditions in other bipolars.

Effects of Annular Surround Backgrounds on Bipolar Sensitivity

The preceding three expreriments provide a framework in which to view the behavior of the bipolar cell center *response* under a variety of background conditions. Surround backgrounds appear to affect the entire intensity-response function for the bipolar center. The following experiments are designed to verify an interpretation of these data through which bipolar *sensitivity* can be evaluated as a function of background illumination. The interpretation is based on the assumption, formalized in the discussion, that sensitivity at any fixed test intensity region, is related to the slope of the intensity-response curve at that intensity.

If sensitivity is related to the slope of the bipolar response curves, then it should be highest for incremental test stimuli with intensities that intersect the steep midportion of the log-intensity response curves. To test this, I have presented a flickering stimulus to the center of the bipolar cell receptive field, and then moved the log-intensity response curves to different relative positions along the intensity axis with respect to the flicker by varying the level of surround background. The surround background was, in all cases, an annulus with 0.5-mm inside diameter, and 1-mm outside diameter. In a sense, the flicker stimulus is a probe of the slope of the response function, but the flicker also represents a form of incremental stimulus with which to evaluate the center sensitivity.

Representative experiments, demonstrating a form of sensitization and desensitization by surround backgrounds are shown in Figs. 9 C and 9 A, respectively. These curves show the *time-course* of the response to the flicker stimulus before, during, and after the presentation of the surround background. Figs. 9 B and 9 D are taken from Fig. 7 to suggest the concomitant effect of the surround background in the *intensity* domain. In 9 B the flicker was initially aligned with the steepest part of response curve *a*), eliciting a flicker response (*a*) in 9 A. The surround background then shifted the response curve to position *b* in 9 B; in misalignment with the flicker. As a result, the flicker response in 9 A was reduced (*b*) in the presence of the surround background. This experiment simply shows that the surround background shifted the log-intensity response curve to the right, and reduced the incremental response which is a measure of the sensitivity of the bipolar center.

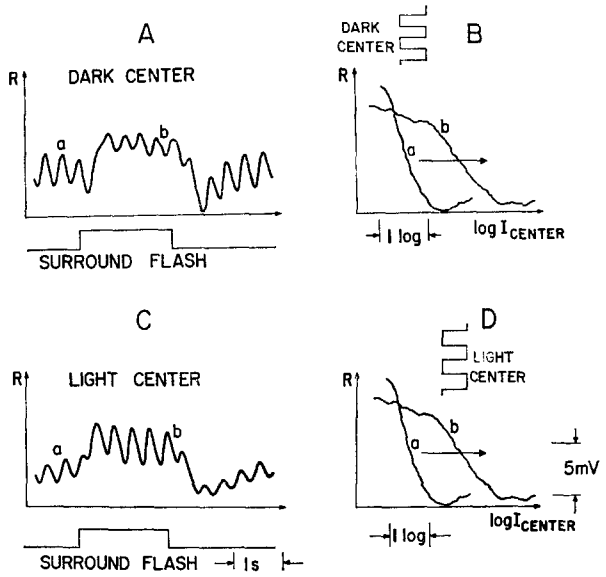


FIGURE 9. Sensitization and desensitization by annular surround backgrounds. A and C show time-course of flicker response when surround background is added for 1 s. B and D show the effects of the background on flicker, interpreted in the intensity domain. In experiment A-B, the flicker is initially aligned with curve *a*, so when the surround shifts the curve to *b* the response to flicker is reduced. In experiment C-D, the flicker is initially aligned with curve *b*, so when the surround shifts the bipolar operating curve to *b* the response to flicker is enhanced.

In the experiment represented by Figs. 9 C and 9 D, the conditions between flicker and response curves were reversed and the surround served to sensitize the center. Initially, the flicker stimulus was aligned with response curve *b* in 9 D, but in the absence of the surround, the bipolar was still operating with curve *a*. Since the flicker stimulus intensities were misaligned with operating curve *a*, the flicker response was relatively small and strongly hyperpolarized as shown by *a* in 9 C. The surround background served to shift the operating curve from *a* to *b* in 9 D, thereby aligning it with the flicker stimulus intensities so the magnitude of response in the presence of the surround background was increased and the cell depolarized as shown by *b* in 9 C.

The pair of experiments suggests that the surround background can either sensitize or desensitize the center of the bipolar cell receptive field, depending upon the relative alignment of the center response function with the center incremental intensities. The experiment rules against scatter from the surround as a mechanism for the surround effect since the bipolar center can be sensitized with background as shown in Fig. 9 C. However, this experiment does not establish the site of the sensitization-desensitization mechanism. The lateral antagonistic interactions that realign the bipolar cell response curves

could either be fed back to receptors, fed forward to bipolars, or mediated by some other synaptic pathway.

The experiments give some indication as to the time-course of the curve shifting phenomenon. The flicker rate was about 3.5/s, and the change in magnitude of response to flicker seems to be complete within one cycle of flicker. Therefore, the change in magnitude probably accompanies the change in response level mediated by the antagonistic surround, and is comparable to the time-course of horizontal cell response of 200–300 ms.

Fixed Response Limits for the Bipolar Cell

The bipolar response curves in Fig. 2, 7, and 8 are of constant overall magnitude, regardless of their position along the log-intensity axis. These limits may represent saturation levels that can also serve to reduce sensitivity. This experiment explores the saturated bounds related to sensitivity measurements. Fig. 10 illustrates an experiment similar to that shown in Fig. 9, but where the modulation depth of the stimulus was much greater (about 1 log unit) and the surround intensity was *gradually* varied over a wider range. Initially, with no background surround, the bipolar was presumably operating on curve *a* in Fig. 10 B, and the response to flicker is shown by the initial portions of the upper curve in 10 A. The surround background was gradually increased, slowly shifting the response curve from position *a* to position *b* thereby misaligning the operating curve with the flicker. As a result, the bipolar response was compressed against a fixed upper bound as shown in 10 A. In a second ex-

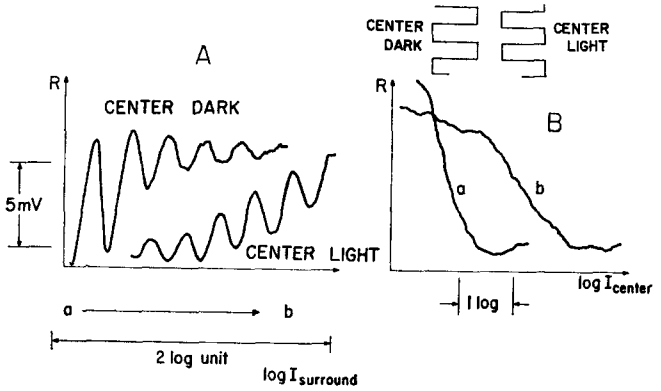


FIGURE 10. Saturation and unsaturation of flicker response. The protocol is the same as in Fig. 9, except that the intensity of the annular *surround* was increased gradually instead of being flashed, shifting the operating curve for the hyperpolarizing bipolar from *a* to *b*. The "center dark" flicker was initially aligned with curve *a*; "center light" flicker was aligned with curve *b*. The response increased and "unsaturated" in magnitude when the operating curve for the hyperpolarizing bipolar was brought in alignment with the flickering stimulus.

periment, given by the lower curve in Fig. 10 A, the bipolar center was illuminated with a brighter stimulus, thereby hyperpolarizing the cell to its limit. As the surround background was increased the bipolar was brought out of saturation and the response magnitude to flicker increased.

This experiment is an extension, in the saturating limit, of the results shown in Fig. 9. Here, the flicker response is reduced by a change in the slope of the response curve, because the bipolar cell seems to saturate. Again, the upper curve in Fig. 10 A shows that the surround desensitizes the center. The lower curve, in which magnitude of response increased with increasing surround, is an example of a sensitizing effect.

Surround Antagonism: A Subtractive Form of Interaction

Some of the previous experiments show that the log-intensity response curve for the bipolar cell is displaced parallel to its original position along the log-intensity axis in the presence of surround illumination. This suggests either that the surround acts to *attenuate* the signal reaching the bipolar cell by a constant multiplicative factor, or that the surround *subtracts* a constant quantity from this signal. An attenuation of the signal would result in a parallel displacement of the curves if, as in the case of the cones (Normann and Werblin, 1974) it occurred at an initial stage of transduction, but a subtractive effect could displace the curves if it acted, say, at the receptor terminal. These alternatives will be considered more formally in the Discussion; the following experiment supports the hypothesis that surround antagonism in the bipolars is a subtractive phenomenon.

Fig. 11 A illustrates an experiment in which the receptive field center of a depolarizing bipolar cell was stimulated with a spot of 1.1-log units intensity, modulated to a depth of 0.1 log units. The time-course of the response is shown, where at second 1 the center stimulus was presented, depolarizing the cell (*a*). At second 2 the surround annulus was introduced, thereby reducing the depolarization (*b*). At second 3 the surround was terminated, once again depolarizing the cell (*c*), and at second 4 the center stimulus was terminated (*d*). The important point here is that although the surround reduced the *level* of polarization by more than 50%, the modulated response to flicker was not, noticeably altered, suggesting the surround *subtracts* a constant quantity.

Fig. 11 B illustrates the relationship between the flicker stimulus and the bipolar response curves in the intensity domain. The response curve for the bipolar was shifted to the right by the annulus, but the flicker stimulus always fell along the steeper portions of the curves. This experiment can be considered as a test, in the time domain, of the degree to which the displaced response curves are parallel. The relatively constant response to flicker, at different polarization levels in 11 A is a confirmation of constant slope of the curves in 11 B.

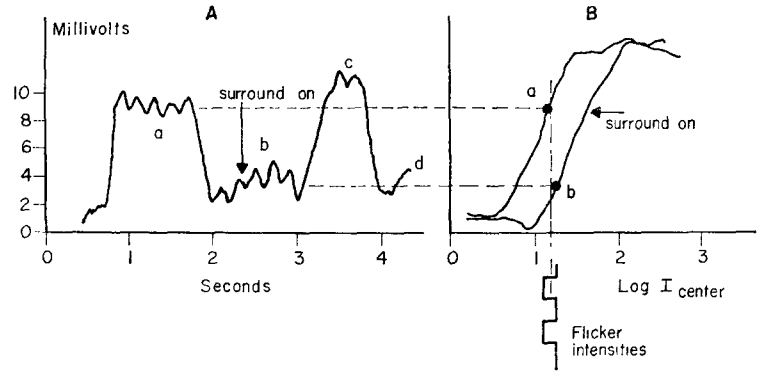


FIGURE 11. Subtractive nature of the annular surround. The protocol is the same here as in Figs. 9 and 10 except that the modulation depth of the flicker is low, at 0.1 log units. (A) Time-course of response to flicker; (B) interpretation of the time-course in the intensity domain. In A, the flicker stimulus is presented at *a*, then the surround is introduced at *b*, then removed at *c*. Finally, the flicker stimulus is removed at *d*. The surround reduces the magnitude of the bipolar response by about 50%, but does not affect the magnitude of the flicker response. In B, the flicker intensities are always aligned with the linear portions of the log intensity-response curves.

DISCUSSION

Lateral Interactions: Contrast Detection or Adaptation?

Earlier reports (Werblin and Dowling, 1969; Werblin, 1970 and 1971) suggested that the lateral interactions at the outer plexiform layer served a contrast-detecting function. Since annular illumination, presented at the surround of the bipolar cell receptive field tended to antagonize the response elicited by illumination at the center, the change in maintained polarization in the bipolar cell was smaller when the field was *uniformly* illuminated than when a contrasting boundary illuminated the receptive field. Lateral interaction mediating this contrast function may be a general property of visual systems; similar results have been reported for the first level of neural processing in an invertebrate retina (Ratliff, 1965).

However, this view of bipolar function should probably be modified to include the effects of the surround on the full range of bipolar response. Although the steady level of polarization in the bipolar is an antagonistic function of illumination at center and surround of its receptive field, the incremental *change* from that level, elicited by a change in the configuration of stimulus pattern, is probably a more important property of the response as shown in the following paper (Werblin and Copenhagen, 1974). The present experiments suggest that the antagonistic surround serves to optimize the magnitude of incremental response to change of stimulus in the bipolars and thereby enhance sensitivity. When the surround is illuminated, the entire intensity response

curve for the center of the bipolar receptive field is repositioned in the log-intensity domain. The steepest and therefore the most sensitive portion of this center-response curve can be aligned with different center intensities determined by the level of *surround* illumination. Under special experimental conditions the surround can serve to either sensitize or desensitize the center of the bipolar receptive field depending upon the relative alignment of the response range with center intensities (Fig. 9).

By this argument, the lateral antagonism that forms the surround of the bipolar cell receptive field serves as a second stage of adaptation, concatenated with the adaptation in the photoreceptors. In the following I try to infer the nature of the input-output function from photoreceptors to bipolars, as modified by the horizontal cell system, and derive a measure of sensitization.

Input-Output Function for the Outer Plexiform Layer

A schematic representation for the general connections between the neural elements associated with the outer plexiform layer is given in Fig. 12 A. It is possible to derive a graph of the relationship between receptor and bipolar cell activity, and to show how that relationship is affected by different levels of horizontal cell activity, because the separate influences of horizontal cells and receptors upon bipolar cell activity can be isolated in both space and time. The experiment illustrated in Fig. 6 shows that the bipolar cell is excited over a narrow region of the retina; probably not more than 300 μm in diameter, but the horizontal cells exert their antagonistic effect on bipolar activity over a broad retinal region covering up to 2 mm. The experiment also shows that the antagonistic effect from the surround is delayed by about 250 ms. Therefore, bipolar activity, elicited by the receptors, but unaffected by horizontal cell antagonism can be measured either with a small spot centered upon the bipolar cell receptive field as in Fig. 7, or derived at a time before the onset of surround antagonism as in Fig. 2. The bipolar cell intensity-response curves, derived by either of these methods are quite similar and differ from those of the receptor (Normann and Werblin, 1974) and horizontal cells (Fig. 1) in that the graded bipolar response spans a narrower range of log intensity, and can be aligned with different absolute ranges of log intensity as a function of surround illumination.

Fig. 12 B, C, and D illustrates a technique for evaluating the relationship between receptor and bipolar activity, and shows how this relationship is affected by horizontal cell activity. In terms of the diagram in Fig. 12 A, Fig 12 C is a graph of b versus a for two values of c with log I as the implicit parameter. I used the pair of bipolar curves shown in Fig. 11 here, and since these were derived under scotopic conditions, I compared the activity of this bipolar (graph B) with a rod curve (graph D) taken from the previous paper (Normann and Werblin, 1974, Fig. 2). For each test intensity I plotted the

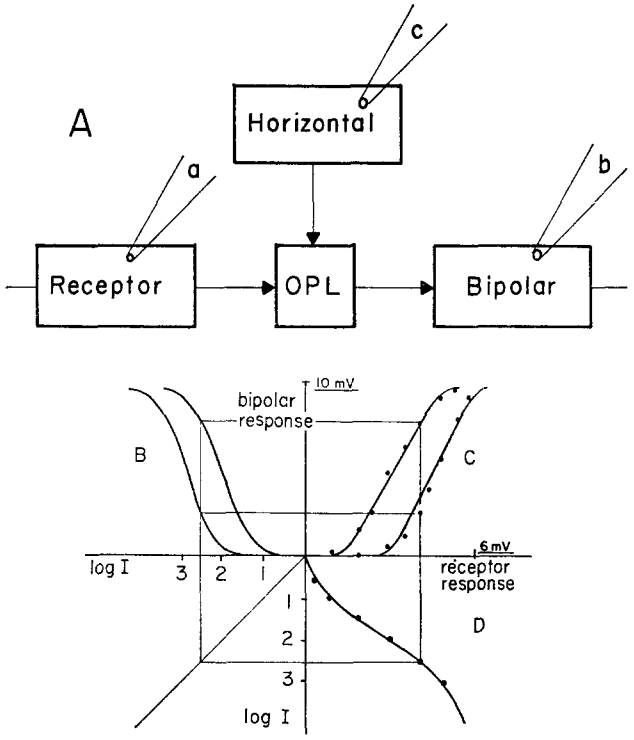


FIGURE 12. (A) Schematic of the system of connections at the outer plexiform layer, (OPL). Both receptor and horizontal activity enters the OPL and the resultant interactions are "read out" by the bipolar cell. The pipettes indicate the signals to which we have access. (B) The intensity-response curves for the bipolar taken at two surround backgrounds from Fig. 11. (D) The intensity response curves for a rod, under similar conditions taken from the previous paper. (C) Plot of the bipolar response versus receptor activity for two surround backgrounds in the scotopic range. Curves C were derived by selecting a stimulus intensity, shown as 2.5 log units in the figure and plotting the bipolar response (ordinate) against the receptor response (abscissa) elicited at the same intensity. The curves were completed by plotting bipolar activity against receptor activity at many different values of log I for two different surround intensities.

magnitudes of response at two surround backgrounds for the bipolar (B) against that of the receptor (D). This procedure generated a pair of curves (C) relating peak bipolar activity to peak receptor activity for two different levels background illumination. I cannot be sure that the test intensities of each corresponding pair of points on graph C were identical in the experiments, but the form of the curves is not critically dependent on this alignment.

Each of the bipolar curves in Fig. 12 C spans less than the full range of response for the receptors, but the bipolar response can be aligned with different subregions of the receptor response range by varying the surround illuminance. This suggests that the bipolar response magnitude is limited at a site proximal

to that of the receptor, probably at the bipolar membrane itself, and that the surround effect is introduced before the receptor signal reaches the bipolar membrane, perhaps at the receptor terminal. This is consistent with Baylor et al. (1971) who show a presynaptic effect (with respect to bipolars) for the horizontal cells in turtle, and with Nelson (1973) who suggests, from measurements of the electrical properties of the bipolar membrane, that the surround effect is not postsynaptic.

The curves in Fig. 12 express the cumulative effects of a series of transformations that lead to the bipolar response, and they suggest a mechanism for the lateral antagonism at the surround of the bipolar receptive field that displaces the response curves. The graphs in 12 C show, on linear coordinates, the relationship between peak receptor activity and bipolar activity at two different surround levels. Surround illumination alters this relationship such that over most of the bipolar response range, the receptors must polarize by an additional 3 mV to elicit the same bipolar response. If the lateral antagonism acts at the outer plexiform layer near the receptor terminal, then it seems to *subtract* a constant quantity, corresponding to 3 mV in the receptors, from the receptor-to-bipolar signal. An *attenuation* of this signal at the outer plexiform layer would tend to alter the slope of the input-output curves in graph 12 C. The subtractive nature of these interactions is supported by the experiment in Fig. 11 where surround illumination altered the level but not the magnitude of the flicker response.

Sensitization and Desensitization by Surround Backgrounds

As in the previous paper, sensitivity can be defined as the change in response versus stimulus increment,

$$S\alpha \frac{dV}{dI},$$

where S is sensitivity, dV is the change in response, and dI is the stimulus increment. This expression can be rewritten to correspond more closely with the log-intensity response curves used in these experiments as

$$S\alpha \frac{dV}{d \log I} \cdot \frac{d \log I}{dI} = \frac{dV}{d \log I} \cdot \frac{K}{I},$$

where K is a constant. Each factor in this expression is related to a specific property of the bipolar intensity-response curves as illustrated in Fig. 13. For a family of bipolar response curves that shift parallel to each other, the slope of all the curves at any criterion response level will be constant as shown in Fig. 13 A. With constant slope, the above expression becomes

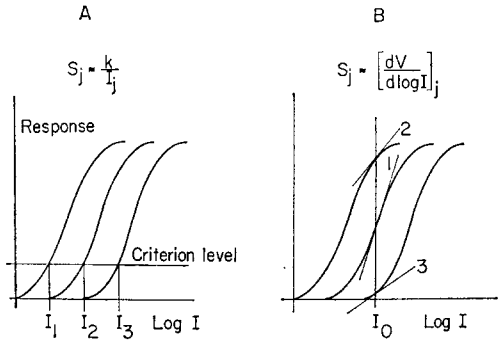


FIGURE 13. Components of sensitivity in the log intensity-response curves. (A) If curves shift parallel to each other along the log intensity axis, and threshold is measured as a fixed criterion level from a fixed base line, then sensitivity is proportional only to the reciprocal of the criterion intensity because the slope of the curves is constant. Sensitivity decreases monotonically from k/I_1 to k/I_2 to k/I_3 as the curves shift to the right. (B) Sensitivity measured at a fixed intensity level, I_0, is proportional to the slope of the curves at I_0. Sensitivity decreases from 1 to 2 to 3, but this is not the order in which the curves shift. If background shifts the curve from left to center in B, the slope at I_0 is increased, and the unit is sensitized by the background.

$$S\alpha \frac{K}{I}; \qquad \frac{dV}{d \log I} = \text{constant},$$

where I is the projection to the intensity axis for each criterion measurement. Curves such as these were generated by simply increasing the surround background level in Figs. 7 and 8. However, it is possible to fix the second term and vary only the first in the expression above as illustrated in Fig. 13 B. Here the value of I is constant, but the slope of the curves at I varies as the curves are shifted by the annular surround background. Under these conditions the above expression becomes

$$S\alpha \frac{dV}{d \log I}; \qquad \frac{K}{I} = \text{constant}.$$

This was the protocol for the experiments illustrated in Figs. 9, 10, and 11, where the flicker stimulus was used to measure the slope of the response curves at a fixed intensity along the log I axis.

Under the conditions specified by Fig. 13 A, the decrease in sensitivity is a monotonic function of surround illumination because the curves are continuously shifted to the right by background. However, under the conditions of Fig. 13 B, the sensitivity is *not* monotonic with surround illumination because the slope of the individual response curves is low at either end and high in the center. Therefore, it is theoretically possible, to either increase or de-

crease sensitivity at the center of the bipolar cell receptive field by increasing the surround background in the presence of a fixed center intensity.

Crawford (1940) and Ratoosh and Graham (1951) showed psychophysically that as the diameter of a background disk was increased, threshold at the center of the disk first rose and then decreased, suggesting that the outer regions of the disk served to *sensitize* the center. Westheimer (1965) studied the sensitizing effect of separate annulus upon a center test area where threshold had been elevated by a background spot. More recently Ikeda and Wright (1972) have shown that an annulus can serve to enhance the response to a central test flash in cat ganglion cells, and Copenhagen (1972) has demonstrated similar effects in the ganglion cells of mudpuppy.

These observations raise the possibility that the sensitizing annulus serves a "disinhibiting" function, as suggested by Ikeda and Wright (1972). A surround can disinhibit within a single stage of lateral interaction only if it operates in the recurrent, or feedback mode as demonstrated in *Limulus* (Ratliff, 1965). Therefore the sensitization experiments could be used to test for disinhibition, and the finding of disinhibition would suggest that the pathway for lateral interactions was recurrent. Recently, Copenhagen (1972) and Burkhardt (1974) have shown that the response of horizontal cells in mudpuppy can be augmented by a surround, thus implicating feedback connections with receptors, and confirming this, Witkovsky et al. (1973) have shown that the PIII component of the electroretinogram in fish which is probably of receptor origin, can be augmented by an annular surround.

The results shown in Figs. 9 C and 10 A suggest that sensitization results not from disinhibition, but from direct surround antagonism. The bipolar cells were sensitized because the nearly saturating response due to center illumination alone was reduced by the surround background. This aligned a steeper region of the log intensity-response curve with the center stimulus intensities thereby allowing a greater response magnitude for a given incremental stimulus at the center.

Since the lateral antagonistic signal is probably fed back, at least in part, to the photoreceptors, the possibility for disinhibition exists at the outer plexiform layer. However, it has been difficult to demonstrate a true disinhibitory phenomenon at the bipolar cell level.

Intensity-Response Functions

We showed earlier (Normann and Werblin, 1974) that the intensity-response function for the photoreceptors in mudpuppy can be approximated by the relation, originally suggested by Naka and Rushton (1967) of the form

$$\frac{V_r}{V_{r_m}} = \frac{I^n}{I^n + k^n},$$

where V_r is the receptor response, V_{r_m} is the maximum response (for normalization), I is the stimulus intensity, and k is the intensity at which $V = \frac{1}{2} V_{r_m}$. The value of n is a function of the stimulus duration, being about 0.7 for long test flashes (seconds) and 1.0 for short test flashes (10 ms). These functions have been used to approximate the responses for receptors in turtle, (Baylor and Fuortes, 1970), primate (Boynton and Whitten, 1970), skate (Dowling and Ripps, 1972), and mudpuppy (Normann and Werblin, 1974) as well as horizontal cells or S potentials in tench (Naka and Rushton, 1967), and cat (Steinberg, 1969), and skate (Dowling and Ripps, 1971).

The intensity-response function for the bipolar cell, when only the center of its receptive field is illuminated, is best fit with the above expression but when the exponent is about 1.2, a higher value than that given for any of the more distal cells. On the other hand, if the plateau of the response after 250 ms during a difluse flask is plotted versus intensity, the curve is best fit with the above expression having an exponent less than 0.5 at scotopic levels, and zero in the photopic range (Fig. 5).

The differential input, tending to limit the steady state response was predicted by Barlow and Levick (1969) in their study of cat ganglion cells. They showed that the spontaneous activity did not increase in a simple way as background level was increased. They suggested that a differential mechanism is useful in the cat for limiting the rate of spike discharge while maintaining sensitivity. It is similarly useful in the mudpuppy for limiting the level of bipolar potential while maintaining the steep constant slope of the log-intensity function, as illustrated in Figs. 7 and 8. Some of the adjustment in DC level seems to take place in the photoreceptors themselves as shown in the accompanying paper.

Where do Horizontal Cells Exert their Antagonistic Effect?

The derivation above makes no assumptions about the site of antagonistic interactions from horizontal cells, but is consistent with the observations of Baylor et al. (1971) and Nelson (1973) suggesting that horizontal cells feed back to the receptors. However, a comparison of the time-courses of response for the horizontal cells and bipolars, as shown in Figs. 3 and 4, suggest that something more is happening. The waveforms of response to diffuse flashes at similar background levels show that after about 250 ms the bipolar response is greatly reduced in magnitude, whereas the horizontal cell response remains relatively sustained. The experiment in Fig. 6 shows that the bipolar response is reduced as a function of horizontal cell activity. If horizontal cells fed back to the receptors to mediate the antagonistic effect, then the receptor signal should also be reduced with a time-course resembling that of the bipolars. A reduction in receptor signal ought to be reflected in the activity of the hori-

zontal cells presumably driven by receptors. That the horizontal cells do not "turn off" after 250 ms like the bipolars, in response to a diffuse flash, suggests that much of the antagonistic effect measured in the bipolars is either not fed back to the receptors, or does not influence the receptor signal that specifically drives the horizontal cell.

SUMMARY

(a) Background illumination, presented to the surround of the bipolar cell receptive field, initiates lateral interactions that modify the bipolar response to test stimuli presented at the center of the field. (*b*) The effect of the surround can be isolated from the center response because it is slower by about 250 ms, extends over a broad retinal area almost 2 mm in diameter, and antagonizes the response to center illumination. (*c*) Although most evidence is consistent with a feedback pathway for the antagonistic surround, an important component of the lateral antagonistic effect may not be fed back to the receptors, but may still be presynaptic to the bipolars. (*d*) A fixed illuminance in the antagonistic surround reduces the magnitude of the center response by a constant quantity regardless of the level of center response. This suggests that the surround subtracts from the center. As a result, the entire log intensity-response curve for the bipolar appears to be shifted without change of slope along the log intensity axis by surround illumination. (*e*) The antagonistic surround aligns the graded response range of the center of the bipolar cell receptive field with different levels of center test intensities. Therefore, the bipolar cell is sensitized by the surround when the steepest portion of its intensity-response function is aligned with the center test intensity level.

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