

## B-WAVE CURRENTS IN THE FROG RETINA

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**Abstract**—*B*-wave current flow was analyzed using resistance values and *b*-wave amplitudes measured as a function of depth within the vitreous, retina and choroid of the frog eyecup. This current arose from a proximal current source which was restricted to a narrow region bordering the inner limiting membrane, and a diffuse current sink, which had two prominent peaks, one in the distal retina and the other in the proximal retina. This source density distribution suggests that Müller cells are involved in the establishment of the *b*-wave response.

### INTRODUCTION

The electroretinogram (ERG) of the vertebrate eye was first analyzed with intraretinal microelectrode recordings by Tomita in 1950. The technique has proved valuable and has been employed by many workers to investigate the cellular origin of the *b*-wave response, a prominent component of the ERG.

Tomita and his colleagues recorded the intraretinal *b*-wave at different depths within the bullfrog eyecup (Tomita, 1950; Tomita and Funaishi, 1952; Tomita and Torihama, 1956). Similar studies have since been made by Brown and Wiesel (1961) and Arden and Brown (1965) (among others) in the intact eye of the cat. These investigations showed that the intraretinal *b*-wave has a maximal negative amplitude in the distal retina near the outer plexiform layer.

The first measurements of intraretinal *b*-wave currents were made by Byzov (1959), who corrected his intraretinal voltage measurements for differences in radial retinal resistance. Since then, careful analyses of *b*-wave currents have been made by Faber (1969) and Proenza and Freeman (1975). Faber's results indicate that, in the rabbit, the *b*-wave is primarily generated by a distal current sink and a more proximally located diffuse current source. The work of Proenza and Freeman (1975) indicates that the response in the mudpuppy arises from two separate sinks of current, one in the distal and the other in the proximal retina, both having widely distributed current sources.

The source density study of Faber (1969) confirmed earlier investigations (Tomita and Torihama, 1956; Brown and Wiesel, 1961), showing that the *b*-wave amplitude, which reaches a minimum in the distal retina, rises monotonically to a maximum value near the vitreal retinal surface. These studies emphasized the distal changes in *b*-wave current associated with the minimum of the response. In contrast, the *b*-wave maximum occurring near the inner limiting membrane was largely overlooked (but see Arden and Brown, 1965; and Brown, 1968, who discuss its impli-

cations). Yet the changes in *b*-wave current associated with this maximum response are potentially as significant as the changes occurring in the distal retina.

This study investigates the changes in *b*-wave current which occur near the retinal surface. Measurements of resistance and *b*-wave amplitude within the retina (which have been made in previous studies) have been extended into the vitreous and past the pigment epithelium into the choroid. Analysis of the results suggests that in addition to a distributed current sink which extends through most of the retina, there is a large *b*-wave current source located near the inner limiting membrane.

### METHODS

The eyecup of the northern leopard frog, *Rana pipiens*, was used. Dark-adapted eyes were cut under dim red illumination, as previously described (Newman and Lettvin, 1978).

Two different recording configurations were used to achieve high and low levels of extra-retinal current flow. In the first series of experiments, eyecups were placed on a piece of Ringer's-soaked gauze (Fig. 1A). Under these conditions, extra-retinal current flow was low, due to high vitreal-to-scleral resistance. In a second series of experiments, eyecups were submerged under Ringer's solution (112 mM NaCl, 2.4 mM KCl, 4.0 mM NaHCO<sub>3</sub>, 1.0 mM MgCl<sub>2</sub>, 0.9 mM CaCl<sub>2</sub>) as illustrated in Fig. 1B. The eyecups were sealed with vaseline to a lip at the bottom of a Plexiglas cylinder. Extraretinal current flow was relatively high under these conditions, due to the low shunt resistance of the Ringer's solution. Current passing between the proximal surface of the retina and the sclera was constrained to flow over the top edge of the cylinder. Thus, current flow near the retinal surface in the vitreous was directed approximately normal to the surface. In all cases, experiments were conducted within an outer chamber ventilated with moist 95% O<sub>2</sub> and 5% CO<sub>2</sub>. All preparations were maintained at 15°C.

Intraretinal *b*-waves were recorded between Ringer's-filled micropipettes in the retina (~3 µm tip diameter) and in the vitreous (~20 µm tip diameter). The tip of the vitreal electrode was placed within 100 µm of the retinal surface and within 200 µm of the entry point of the vertically oriented intraretinal electrode. Movement of the intraretinal electrode was controlled by a stepping motor linked directly to a micromanipulator. This facilitated smooth electrode movement within the retina.

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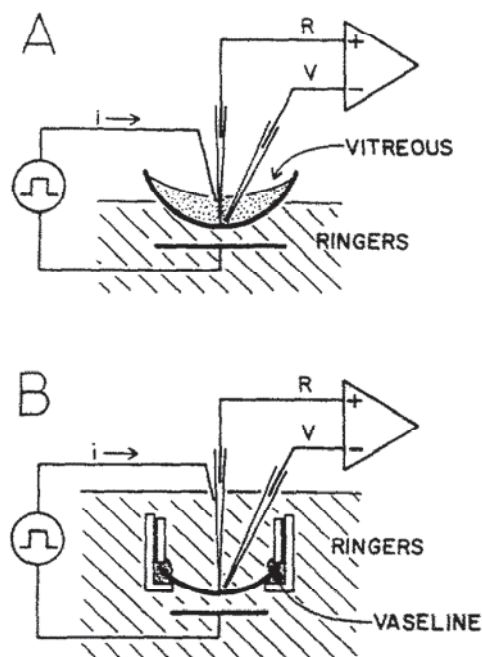


Fig. 1. Diagrams of the two recording configurations. Constant current pulses from a current generator (at the left) are passed through Ag/AgCl wires. Intraretinal *b*-waves are recorded differentially between intraretinal (R) and vitreal (V) electrodes. (A) High shunt resistance. The eyecup is supported on Ringer's-soaked gauze. (B) Low shunt resistance. The submerged eyecup is sealed with Vaseline to the lower lip of a Plexiglas cylinder.

The tissue resistance between vitreal and intraretinal electrodes was measured by passing current pulses of a constant amplitude between Ag/AgCl wires on opposite sides of the eyecup (Brindley, 1956). 10  $\mu$ A (approximate) current pulses were used for the experiments done in air (Fig. 1A) while 200  $\mu$ A pulses were used with submerged eyecups (Fig. 1B), where most of the current was shunted through the Ringer's solution. The geometry of the current electrodes, illustrated in Fig. 1, insured that the current flow across the central region of the retina, pigment epithelium and choroid was approximately uniform.

Stimuli consisted of diffuse white light flashes presented in the dark and which illuminated the entire eyecup. Stimulus flashes were 100 msec in duration and were typically 5.7 log units above absolute threshold in intensity. (See Newman and Lettvin, 1978, for a description of the illumination system and of the intensity calibration procedure.) Stimuli were repeated at regular intervals (45 or 90 sec) throughout an experiment, which was begun after the preparation had adapted to the repetitive stimulation.

Intraretinal voltages were amplified and filtered as described previously (Newman and Lettvin, 1978). Measurements of *b*-wave and current pulse amplitudes were made directly from records of a rectilinear, analog pen recorder (Mark 260, Gould, Inc.). *B*-wave amplitudes were measured from the pre-stimulus base-line to the voltage which occurred at a constant delay following the stimulus (corresponding approximately to the peak values). Fixed-delay amplitudes were used rather than peak amplitudes to avoid complications introduced by the differing time courses of the sub-components of the *b*-wave response (Proenza and Freeman, 1975). *B*-wave amplitude measurements were not significantly contaminated by the *a*-wave response, due to the large *b*-wave to *a*-wave amplitude ratio (typically 8:1 in the distal retina). *B*-wave current source density distribu-

tions were essentially the same when the *b*-wave amplitude was measured from the peak of the *a*-wave rather than from the pre-stimulus base-line.

The depths of the retinal layers were determined histologically from cryostat sections of quick-frozen eyecups to provide a rough comparison with physiological measurements. Values were measured as a percent of total retinal depth with the inner limiting membrane representing 0% retinal depth and the inner face of the pigment epithelium 100% retinal depth. These values varied widely in different regions of the eyecup and should only be considered as approximations. Average values were: ganglion cell layer, extending from 6% to 10% retinal depth; inner nuclear layer, 32% to 51%; outer nuclear layer, 60% to 69%. It is important to bear in mind that these values are only approximations and cannot be used to accurately localize physiologically determined sources and sinks of *b*-wave current.

## RESULTS

*B*-wave current flow is analyzed in the experiments reported here using the resistance values and *b*-wave amplitudes measured at different depths within the choroid, retina and vitreous humor. In most cases, measurements were made during electrode withdrawal (towards the vitreous) as this produced smoother electrode movement through the retina (Brown and Wiesel, 1961; Faber, 1969). Similar results were obtained when electrodes were advanced through the retina. In all cases, resistance was measured immediately following stimulus presentation at each retinal depth.

A typical plot of *b*-wave amplitude as a function of retinal depth is shown in Fig. 2A. This experiment was performed on an eyecup supported on Ringer's soaked gauze (Fig. 1A). The minimum *b*-wave amplitude occurs at approximately 65% retinal depth. The amplitude rises both proximally and distally from this point with a steep rise in *b*-wave amplitude occurring across the extreme distal retina and pigment epithelium.

Retinal depth shown on the abscissa of this figure was determined by micromanipulator setting, using resistance landmarks as calibration points. The distal margin of the high resistance R-membrane (Brindley, 1956), which is believed to represent the inner face of the pigment epithelium (Brindley and Hamasaki, 1963; Cohen, 1965), was defined as 100% retinal depth. 0% retinal depth (the retinal surface) was taken as the border between the low resistance vitreous and the high resistance retina.

Plots of amplitude vs depth such as illustrated in Fig. 2A do not give an accurate measure of *b*-wave currents due to inhomogeneities in eyecup resistance. These plots can be corrected for changes in resistance by one of two procedures based on the Ohm's law relation,  $I = V/R$ . The change in amplitude measured between each pair of experimental points can be divided by the radial resistance of the corresponding interval. Alternatively, *b*-wave amplitude can be plotted as a function of resistive (not spatial) distance from the retinal surface. In either case, the slopes of the resulting plots will accurately reflect radial current. Straight lines in these plots indicate a constant current flow (in a radial direction). Changes in slope, i.e. a non-zero second derivative, indicate the location of sources or sinks of current.

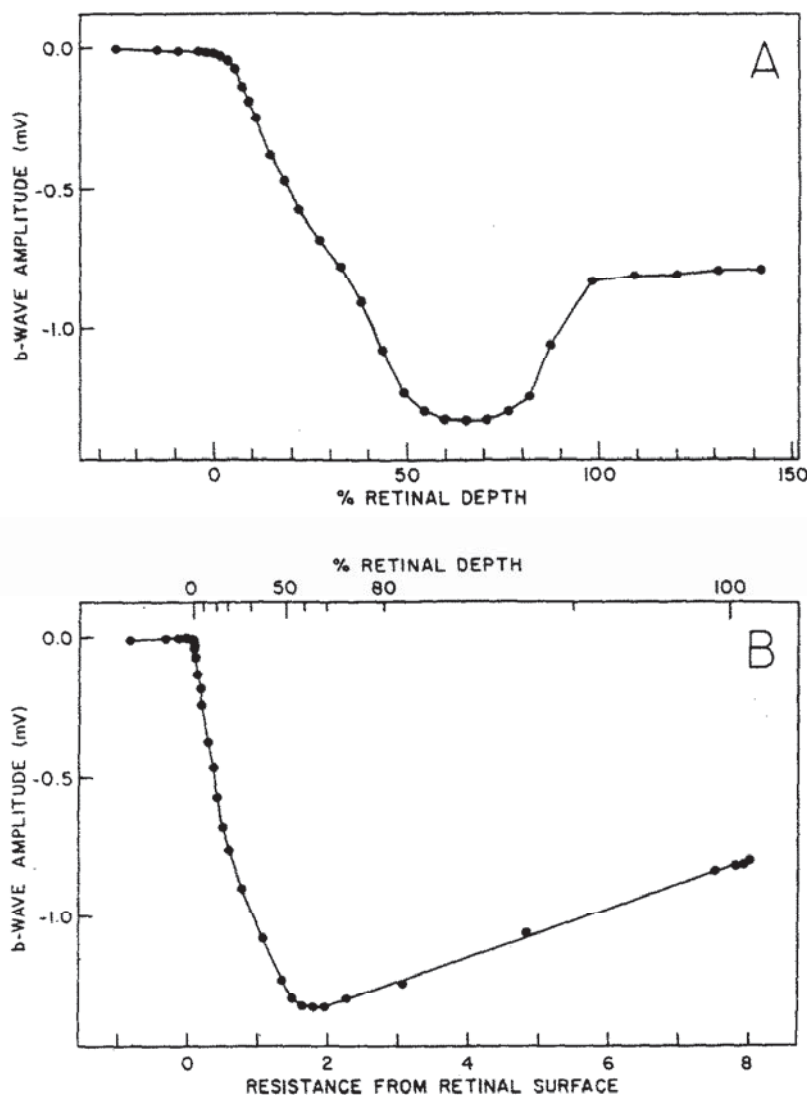


Fig. 2. Intraretinal *b*-wave amplitude as a function of (A) linear depth, and (B) resistance from the retinal surface (in arbitrary units). The eyecup was supported on Ringer's-soaked gauze. 0% and 100% retinal depth points were determined from resistance measurements, as described in the text.

The data shown in Fig. 2A have been replotted in Fig. 2B, using the latter method, with *b*-wave amplitude graphed as a function of resistance from the retinal surface (in arbitrary units). Tissue resistance was determined by applying current pulses of constant amplitude across the entire eyecup (Brindley, 1956). Resistance from the retinal surface was directly proportional to the pulse amplitude measured differentially between intraretinal and vitreal electrodes.

The *b*-wave amplitude curve is simplified when plotted in this manner. As seen in Fig. 2B, the amplitude rises linearly across the distal retina, pigment epithelium and choroid (the right hand portion of the graph), showing that a constant *b*-wave current flows in this region. Proximal to its minimum, the amplitude of the *b*-wave rises in two linear segments, with a change in slope occurring near 30% retinal depth. In addition, *b*-wave amplitude declines slightly in the vitreous.

In the experiment illustrated in Fig. 2 the eyecup was exposed to air (Fig. 1A). The amplitudes of the

*b*-wave measured in the vitreous of this preparation are small due to a low value of extra-retinal current flow. In addition, vitreal current does not flow normal to the retinal surface in this preparation but towards the edge of the eyecup. These limitations can be overcome by using the submerged eyecup preparation shown in Fig. 1B. The low shunt resistance introduced by the Ringer's solution in this configuration increases extraretinal current flow and allows an accurate determination of *b*-wave currents proximal to the retinal surface.

Figure 3 shows a plot of *b*-wave amplitude as a function of resistance from the retinal surface, in a submerged eyecup. This plot of *b*-wave amplitude differs from Fig. 2B primarily in the magnitude of the extraretinal current flow. The rise in *b*-wave amplitude across the distal retina, pigment epithelium and choroid is much greater in this case, indicating that a large extraretinal current flows under these conditions. The fall in *b*-wave amplitude proximal to the retinal surface is also greater in the submerged

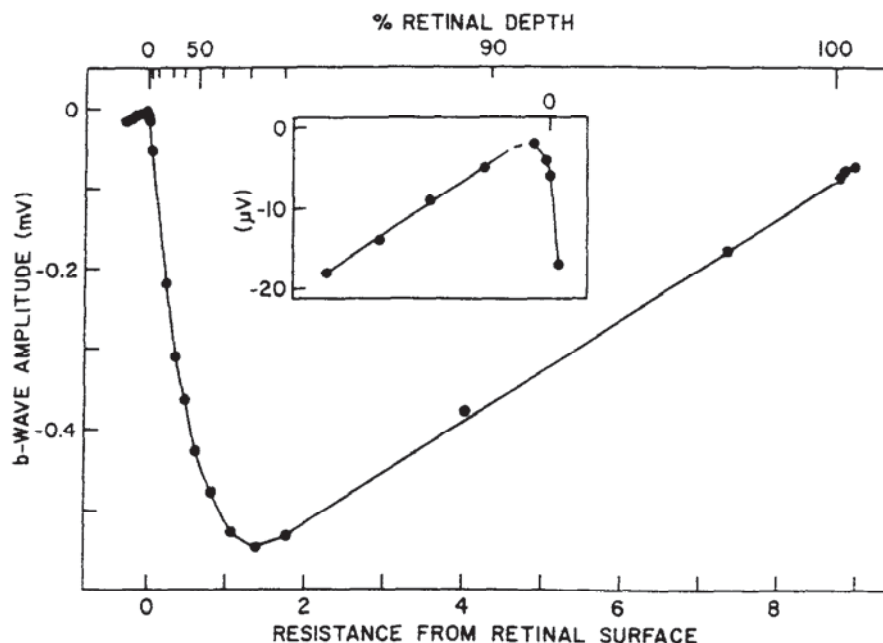


Fig. 3. Intraretinal *b*-wave amplitude as a function of resistance from the retinal surface (in arbitrary units) in a submerged eyecup. Inset shows proximal portion of plot expanded by 10 along both axes. Note that the slopes of the proximal and distal portions of the graph are nearly equal.

eyecup. An expanded view of this portion of the graph is shown in the inset. The slope of the curve proximal to the retinal surface is almost identical to the slope in the distal retina, pigment epithelium and choroid. This demonstrates that the magnitude (and polarity) of *b*-wave current leaving the proximal retina is equal to the current entering the distal retina.

The experiment illustrated in Fig. 3 also demonstrates that *b*-wave current flow (the first derivative of the graph) reverses direction near the retinal surface. Current flows away from the surface in both vitreal and scleral directions. Thus a source of *b*-wave current must lie in this region.

A quantitative measure of the distribution of current sources and sinks can be obtained by calculating the three-dimensional gradient of the current flow within the eyecup. This procedure has been discussed by Howland, Lettvin, McCulloch, Pitts and Wall (1955), Faber (1969) and Nicholson and Freeman (1975). In the uniformly illuminated retina, current flow is essentially restricted to a radial direction. Thus, calculation of source density simplifies to a one-dimensional problem and can be determined by taking the second derivative of the resistance-corrected *b*-wave amplitude with respect to retinal depth.

An analysis of *b*-wave source density of the experiment shown in Fig. 3 is illustrated in Fig. 4. The *b*-wave amplitude has been replotted in Fig. 4A as a function of true (micromanipulator) distance rather than resistive distance. Resistive corrections were made by dividing the *b*-wave amplitude measured between each pair of experimental points by the resistance of the corresponding interval. The distribution of radial *b*-wave current flow is shown in Fig. 4B. It represents the first derivative of the amplitude plot, i.e.  $\Delta b\text{-wave amplitude}/\Delta\text{distance}$ . Figure 4C shows the *b*-wave source density distribution. It was calcu-

lated by taking the derivative (at evenly spaced intervals) of the smooth curve drawn through the points in Fig. 4B. It shows that the *b*-wave arises from a prominent current source near the retinal surface and a distributed current sink with peaks near 30% and 65% retinal depth.

Although the general features of the current source density distribution were similar in all experiments, some variability was seen. The relative amplitudes of the two peaks of the *b*-wave sink varied in different preparations, the distal peak often being larger than the proximal one. As noted by Faber (1969), a small source of current sometimes occurred scleral to the distal peak of the sink. In addition, small current sources were sometimes seen between the two peaks of the current sink, or just vitreal to its proximal peak. The prominent source of *b*-wave current near the retinal surface was seen in all cases.

The exact location of the *b*-wave current source cannot be determined from electrode withdrawal experiments (Figs 2, 3 and 4). As seen in Fig. 4C, the *b*-wave source extends beyond the retinal surface into the vitreous. (This is also illustrated in Figs 2B and 3, where the maximum *b*-wave amplitude occurs proximal to the retinal surface.) Clearly, this localization is erroneous, since the vitreous cannot generate current. It results, most likely, from the retinal surface being pulled into the vitreous as the intraretinal electrode is withdrawn. This leads to tissue distortion and an inaccurate localization of the retinal surface. This problem can be overcome by analyzing *b*-wave current flow while an electrode is advanced from the vitreous into the retina.

One such electrode advance experiment is illustrated in Fig. 5. The upper trace shows *b*-wave amplitude plotted as a function of resistance from the retinal surface. The lower trace plots the position of

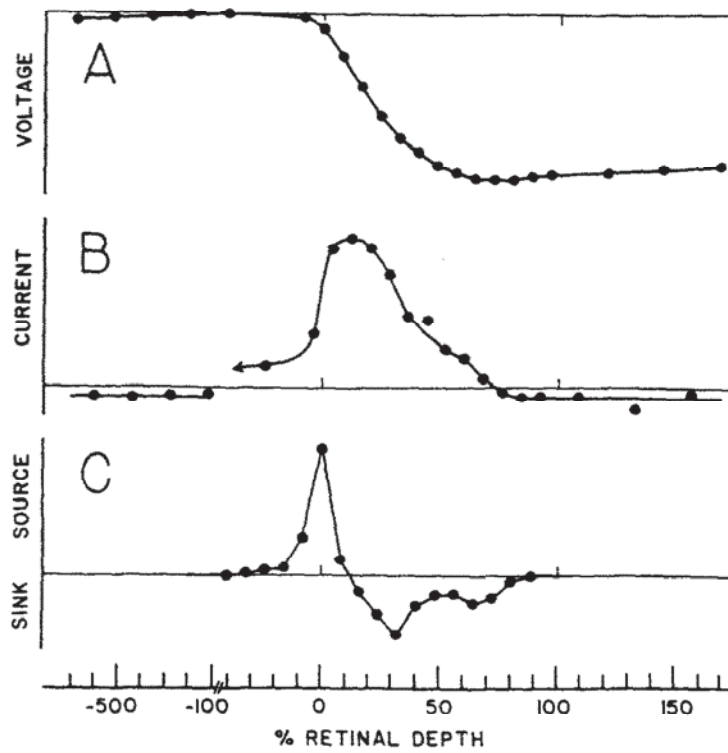


Fig. 4. Source-density analysis of the *b*-wave (from the same experiment illustrated in Fig. 3). The *b*-wave voltage (A), current (B), and source-density (C) are plotted as a function of linear retinal depth. Voltage amplitudes were corrected for resistance by dividing incremental voltage by incremental resistance.

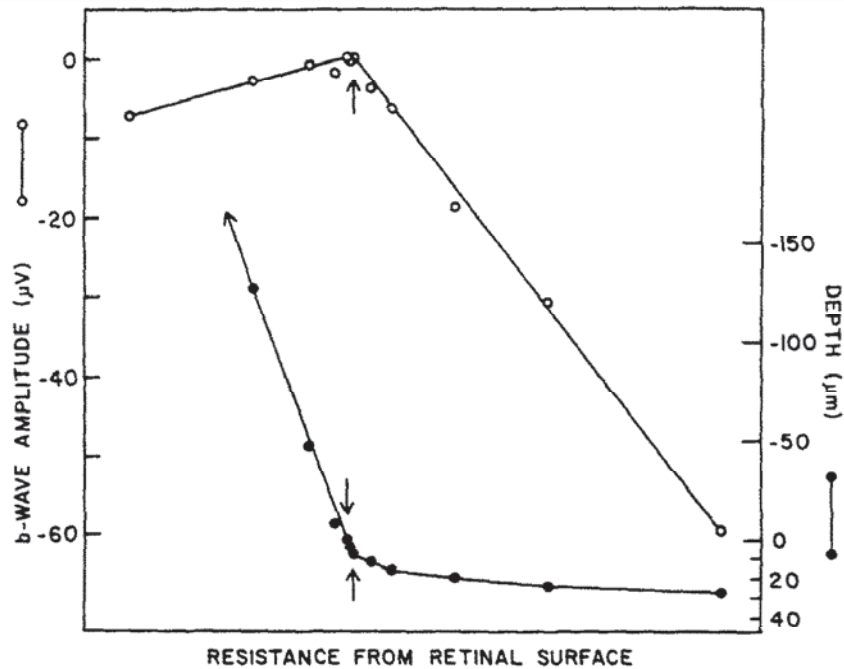


Fig. 5. Localization of the proximal *b*-wave current source. The *b*-wave amplitude (○) and the depth of the intraretinal electrode (●) are plotted as a function of resistance from the retinal surface. The electrode was advanced from the vitreous towards the retina of a submerged eyecup. The downward pointing arrow indicates initial contact with the retinal surface. Upward pointing arrows indicate the point just prior to retinal penetration. See text for details.

the intraretinal electrode (determined by micro-manipulator setting) as a function of the same resistance scale.

The history of this electrode penetration can be read in the lower trace, whose slope corresponds to the value of the radial component of local resistance. Initially, the electrode passes through a region of uniform low resistance (a steep slope) as it advances through the vitreous towards the retina (to the right in the figure). Contact with the surface of the retina, which causes a transient change in the intraretinal electrode voltage (Tomita and Torihama, 1956), is marked by the downward-pointing arrow in the figure. The slope of the curve remains constant during the subsequent two steps (of  $4\mu\text{m}$  each), indicating that the retinal surface was not penetrated. A large change in the slope occurs during the third step, signalling penetration of the retina. (The shallow slope of the plot past this point illustrates that the retina has a higher resistance than the vitreous.)

The position of the electrode just prior to retinal penetration is indicated in both traces by upward-pointing arrows. As seen in the upper trace, *b*-wave amplitude falls from this point in both vitreal and scleral directions, indicating that a current source lies in this region. The first amplitude point following retinal penetration falls along the linear, intraretinal portion of the amplitude curve. This demonstrates that a complete reversal of *b*-wave current occurs within the distance traversed by the first step into the retina. The actual distance traveled by the electrode during its first penetrating step might be larger than the  $4\mu\text{m}$  the electrode was advanced. Nevertheless, this experiment localizes the *b*-wave current source to a narrow region immediately adjacent to the retinal surface.

#### DISCUSSION

The results presented here demonstrate that the *b*-wave of the ERG is generated by a diffuse current sink and a proximal current source. The *b*-wave current sink extends from approximately  $10^\circ$  to  $80^\circ$  retinal depth, and has two distinct peaks, as seen in Fig. 4. The *b*-wave current source is restricted to a narrow region bordering the inner limiting membrane, as illustrated by Fig. 5. This source density pattern is in substantial agreement with the work of Proenza and Freeman (1975) who identified two separate sinks of *b*-wave current in the distal and proximal portions of the retina of the mudpuppy.

The present results differ from Proenza and Freeman (1975), as well as from Faber (1969), however, in showing that the primary *b*-wave current source is restricted to a narrow region bordering the inner limiting membrane. This difference could be due, in part, to species differences. However, the plots of *b*-wave amplitude shown in earlier works indicate that a large, localized current source occurs near the retinal surface in cat (Brown and Wiesel, 1961), rabbit (Faber, 1969) and bullfrog (Tomita and Torihama, 1956) as well.

Such studies show that the intraretinal *b*-wave response rises monotonically in the proximal retina, reaching a maximum value at the retinal surface (Fig. 14 of Tomita and Torihama, 1956; Fig. 3 of

Brown and Wiesel, 1961; Fig. 46 of Faber, 1969). This demonstrates that *b*-wave current flows distally from the surface of the retina in these preparations. Current must also flow proximally from the retinal surface into the vitreous, however, because (a) current leaving the proximal retina must be equal to the current entering the distal retina, and (b) current flows proximally across the distal retina and pigment epithelium. Condition (a), a consequence of Kirchhoff's current law, must be satisfied, because sources and sinks of *b*-wave current occur only within the retina proper. (Figure 4B demonstrates that the current entering and leaving the retina are equal.) Condition (b) is also satisfied, as shown by the monotonic increase in *b*-wave amplitude which occurs distal to its negative peak (Tomita and Torihama, 1956; Brown and Wiesel, 1961; Faber, 1969; see also Figs 2 and 3 of this work). If current flows in both vitreal and scleral directions from the retinal surface, a source of *b*-wave current must lie at the surface.

Arden and Brown (1965), in their study of the intraretinal *b*-wave of the cat, localized the maximum positive *b*-wave response to the inner margin of the inner plexiform layer. They suggest that the positive pole of the *b*-wave dipole (i.e. a current source) lies in this region. However, inspection of their Plate I shows that in three of the five illustrated experiments, *b*-wave amplitude continues to increase up to, or into the optic nerve layer. This location of the *b*-wave maximum is more in accord with the results of the present study.

The findings presented here illustrate the importance of boundary regions in the analysis of current flow. This is particularly true in the retina, which has important cellular structures near its surfaces. As demonstrated in this study, the *b*-wave source density profile can only be determined accurately by extending measurements past the inner and outer limits of the retina proper.

The proximal *b*-wave current source has been accurately localized in electrode advance experiments (Fig. 5). Such experiments demonstrate that the direction of *b*-wave current flow reverses completely within the region traversed by a microelectrode during its first penetrating step into the retina. This localizes the *b*-wave current source to within a distance of probably not more than  $5\text{--}10\mu\text{m}$  from the retinal surface.

Which retinal components generate *b*-wave current? The only elements which lie within  $10\mu\text{m}$  of the retinal surface are the axons and cell bodies of ganglion cells and the proximal foot processes of the Müller cells (Pedler, 1963; Miller and Dowling, 1970). If ganglion cell axons or cell bodies were sources of *b*-wave current, a corresponding current sink would occur in the region of the ganglion cell dendrites, which extend from approximately  $10^\circ$  to  $30^\circ$  retinal depth (see Methods). As seen in Fig. 4, however, the *b*-wave current sink extends to approximately  $80^\circ$  retinal depth. Even the proximal portion of the *b*-wave current sink is probably not generated by ganglion cells, since its maximal amplitude occurs at  $30^\circ$  retinal depth (near the border of the inner plexiform and inner nuclear layers). This suggests that ganglion cells do not contribute significantly to the *b*-wave response. The same conclusion was reached

by Granit (1962), who pointed out that the ERG is not influenced by tetanic stimulation of the optic nerve and that a normal ERG can be evoked following ganglion cell degeneration.

The Müller cell, in contrast, extends from the inner limiting membrane to past the outer limiting membrane of the retina (Cajal, 1972) and is the only retinal element that can account for the observed distribution of *b*-wave source density. The location of the *b*-wave current source corresponds well to the proximal foot processes of the Müller cells (Pedler, 1963; Miller and Dowling, 1970). These processes comprise a 10  $\mu$ m thick layer bordering the retinal surface (measured from Cajal, 1972, Plate 6.1). The diffuse current sink of the *b*-wave, which extends from approximately 10% to 80% retinal depth, lies in the region of the main axial processes of the Müller cells.

This analysis suggests that the distribution of *b*-wave currents is determined by the Müller cells, a conclusion reached by Faber (1969) who first proposed a Müller cell origin of the response in his source density study. Miller and Dowling (1970) have also suggested a Müller cell origin of the *b*-wave. Their work on the mudpuppy demonstrated that the *b*-wave and the intracellular Müller cell response had similar latencies and waveforms and had closely related intensity-response functions.

Faber (1969) and Miller and Dowling (1970) have proposed that the Müller cell response is mediated by increases in extracellular  $K^+$  concentration ( $[K^+]_o$ ) generated by neuronal activity. If the Müller cells are primarily permeable to  $K^+$ , as are other glial elements (Kuffler, 1967), a light-evoked increase in  $[K^+]_o$  would cause a local depolarization of the Müller cell membrane. A current would be established, flowing within the Müller cells from regions of greater to those of lesser  $[K^+]_o$  increase. Current flow through the return current pathway of the extracellular space would give rise to the *b*-wave voltage.

This hypothesis predicts that the *b*-wave current sink should have a similar intraretinal distribution to the light-evoked  $[K^+]_o$  increase, with peaks of the *b*-wave sink associated with neuronal sources of  $K^+$ . Measurements of  $[K^+]_o$ , using  $K^+$ -specific microelectrodes, verify this prediction. Light-evoked increases in  $[K^+]_o$  have been observed within the proximal retina of frog (Oakley and Green, 1976), mudpuppy (Dick and Miller, 1978; Karwoski and Proenza, 1978) and skate (Kline, Dowling and Ripps, personal communication). The source of this  $[K^+]_o$  increase lies near the border of the inner plexiform and inner nuclear layers (Karwoski and Proenza, 1978), a location closely corresponding to the proximal peak of the *b*-wave sink seen in Fig. 4. In addition, light-evoked  $[K^+]_o$  increases have recently been observed within the distal retina of mudpuppy (Dick and Miller, 1978) and skate (Kline, Dowling and Ripps, personal communication). The source of this distal  $[K^+]_o$  increase lies at approximately the same depth as the distal peak of the *b*-wave current sink seen in Fig. 4, near the depth of the maximal negative *b*-wave response (Dick and Miller, 1978).

A source of *b*-wave current should occur near the retinal surface, where light-evoked  $[K^+]_o$  increases are smaller than at deeper locations within the retina. But why is this current source so sharply localized?

This could be a consequence of the Müller cell end foot processes, which are highly invaginated and surround the axons of ganglion cells (Pedler, 1963; Rasmussen, 1974). *B*-wave source current would tend to flow preferentially from this region of increased surface area. A specialization of Müller cell membrane properties in the end foot region, such as an increase in membrane  $K^+$  conductance, could also cause a greater fraction of source current to flow from this area.

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