Principles and Practice of Clinical Electrophysiology of Vision

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Electroretinographic Components Arising in the Distal Retina

Edwin R. Griff

After the onset of steady illumination, the relatively fast a- and b-waves are followed by the c-wave and then by a series of even slower responses that includes a negative deflection (the fast oscillation trough) and a large slow positive deflection (the light peak). Clinically, these slower responses are usually recorded by electro-oculography (EOG), but direct current electroretinography (dc-ERG) has been used experimentally (see Chapters 10 and 21).

The experiments reviewed in this section describe primarily the origins of the c-wave, the fast-oscillation trough, and the light peak of the dc-ERG. The origins of these components involve concentration changes in the subretinal space that in turn produce responses in the cells that border this space, particularly the Müller and retinal pigment epithelial (RPE) cells. These responses are relatively slow and overlap temporally, so the Müller and/or RPE subcomponent voltages sum to produce the recorded dc-ERG component.[29, 46] These subcomponent voltages can be recorded in animal models by positioning a microelectrode in the subretinal space (Fig 9–1).

c-WAVE

The c-wave, a corneal positive potential that follows the b-wave, is the sum of two major subcomponent voltages.[8, 35, 40] These subcomponent voltages have been examined in mammals, birds, reptiles, and amphibians, and the mechanisms of origin are well understood. The accepted model is that a corneal negative subcomponent is generated by the neural retina and a corneal positive subcomponent with a similar latency and time-course is generated by the RPE. In most species, the RPE component is larger, so the resulting c-wave is corneal-positive. The amplitude of the c-wave reflects primarily the *difference* in the amplitudes of the two components, and if the components are equal, the c-wave will be absent (see Fig 9–4,B). This is likely the case in those species (and possibly for some individuals within a species) where the c-wave is small; an example is the cone-dominated retina of the turtle.[30]

Evidence for two c-wave subcomponents comes from several types of experiments. Using a pharmacological approach in the rabbit, Noell[35] showed that the intravenous injection of sodium iodate, which poisoned primarily the RPE, abolished the corneal-positive c-wave and left a corneal-negative potential. In in vitro preparations, a c-wave can be recorded only if the RPE is intact; if the RPE is removed (isolated retina), a corneal-negative response with a similar time course is recorded.[43] Intraretinal microelectrode recordings in the cat,[3] rabbit,[8] monkey,[49] chick,[12] gecko,[15] and frog[37] have confirmed the two subcomponents in both intact and in vitro preparations. An example of such recordings is shown in Figure 9–2. The neural retinal component is commonly referred to as slow PIII.[8]

There is strong experimental evidence that both c-wave subcomponents are responses to the light-evoked decrease in extracellular potassium $[K^+]_o$ that occurs in the subretinal space (the distal $[K^+]_o$ decrease). Measurements of $[K^+]_o$ in the subretinal

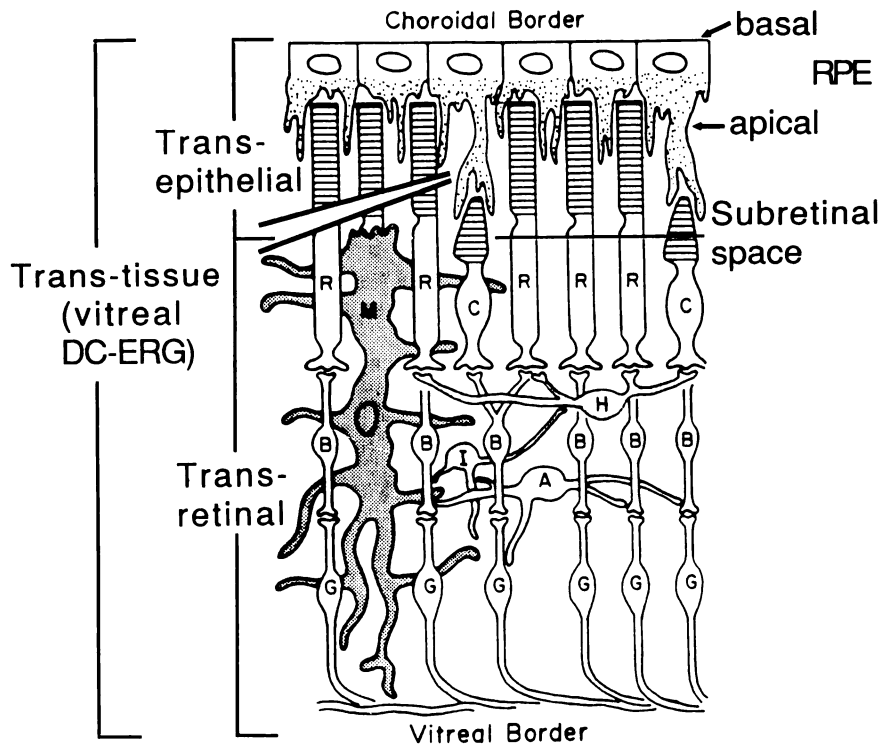

FIG 9–1.
This schematic of a retina shows standard electrode placements. The RPE, photoreceptors (*R* = rods; *C* = cones) and Müller cells *(M)* send processes into the subretinal space. A microelectrode can be positioned in this space, and with reference electrodes behind the eye and in the vitreous, simultaneous recordings can be made of the RPE subcomponent (as a change in the transepithelial potential, *TEP*) and the neural retinal subcomponent (as a change in the transretinal potential). A vitreal ERG is recorded between the vitreous and the choroid. Microelectrodes can also be positioned intracellularly (not shown) to record photoreceptor, Müller, and/or RPE membrane potential changes. For the RPE there are two electrically separated membranes: the apical membrane faces the subretinal space, and the basal membrane faces the choroid. (Adapted from Farber D, Adler R: Issues and questions in cell biology of the retina, in Adler R, Farber D (eds): *The Retina: A Model for Cell Biology Studies*, part I. Orlando, Fla, Academic Press, Inc, 1986.)

space (subretinal $[K^+]_o$) have been made in both intact and in vitro preparations from several species,[15, 24, 30, 38] and the time-course of the $[K^+]_o$ decrease is similar to the c-wave and to each of its components. Blocking K^+ conductance with various agents abolishes both slow PIII[2, 4, 30] and the corneal-positive RPE c-wave.[14, 17]

Müller Cell Component (Slow PIII)

The corneal-negative PIII component of Granit can be separated into a fast component (the late receptor potential, which forms the leading edge of the a-wave) and a slower component, slow PIII. Intraretinal recording at various depths[53] and current source density analysis[8] suggested that slow PIII was generated by a cell that spanned the neural retina. The persistence of slow PIII after aspartate treatment to block postreceptor neuronal responses[52] suggested a Müller cell origin. Additional support for a Müller cell origin is the long integration time, up to 40 seconds in the carp.[52]

The present hypothesis is that the light-evoked subretinal $[K^+]_o$ decrease passively hyperpolarizes the distal end of the Müller cells, and this sets up a transretinal "K^+ spatial buffer" current due to the elongated geometry of the Müller cell. The current drop across the extracellular resistance produces the slow PIII voltage.[6, 8, 19, 52, 54] In support, Karwoski and Proenza[19] recorded a slow hyperpolarization in *Necturus* Müller cells. Recent experiments by Dick and Miller[6] demonstrate the Müller cell hyperpolarization in both the rabbit (Fig 9–3) and tiger salamander[7]; here the time course of the Müller cell hyperpolarization was similar to both the $[K^+]_o$ decrease and slow PIII. Also consistent with the Müller cell hypothesis is the suppression of slow PIII by Ba^{2+} since Ba^{2+} blocks all Müller cell K^+ conductance (E.A. Newman, personal communication) while having little effect on the light-evoked K^+ decrease.[4]

The spatial buffering hypothesis presented above suggests that the transmembrane currents associated with slow PIII may be carried by K^+ and should lead to a reaccumulation of subretinal $[K^+]_o$. Shimazaki and Oakley[41] have described a $[K^+]_o$ reaccumulation that occurs with maintained illumination in detail, but they conclude that it is caused primarily by a slowing of the Na^+-K^+ pump of the photoreceptor.[41] Although some of the details have not yet been resolved, both the generation and the physiological consequences of slow PIII involve interactions between photoreceptors and Müller cells.

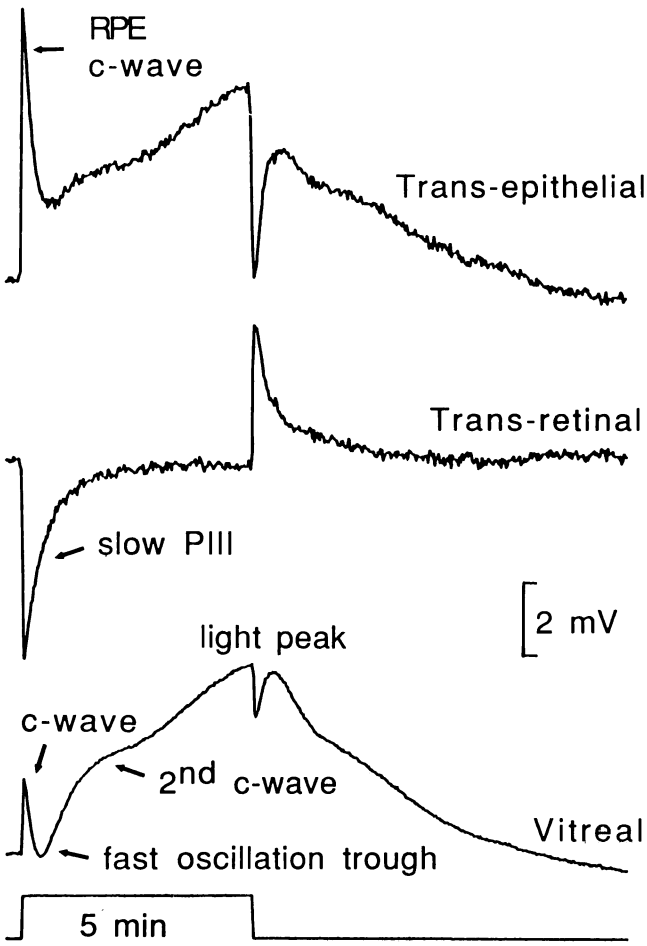

FIG 9–2.
Subretinal recordings from the cat. The vitreal, transretinal, and transepithelial potentials were recorded simultaneously in response to a 5-minute period of illumination. At this slow time scale, the a- and b-waves cannot be seen. In the vitreal ERG a c-wave is followed by a fast oscillation trough and then by a prominent light peak; the shoulder on the rising phase of the light peak is the second c-wave. The intraretinal recordings show that the c-wave has two subcomponents. The initial increase in the transepithelial recording is the large corneal-positive RPE component; the initial decrease in the transretinal recording is slow PIII. For the light peak, only an RPE component is found. (From Steinberg RH, Linsenmeier RA, Griff ER: Retinal pigment epithelial cell contributions to the electroretinogram and electrooculogram, in Osborne NN, Chader GJ (eds): *Progress in Retinal Research,* vol 4. New York, Pergamon Press, 1985. Used by permission.)

Pigment Epithelial Component

The RPE c-wave, a corneal-positive potential recorded across the RPE, results from an increase in the RPE's transepithelial potential (TEP). The RPE has two membranes, apical and basal, and a transepithelial potential exists because the membranes are electrically separated by the high resistance of tight junctions that encircle RPE cells (the "R membrane"). The potentials of the apical (V_{ap}) and basal (V_{ba}) membranes differ, and this difference is equal to the TEP. In every species studied, the apical membrane is more hyperpolarized than is the basal membrane, so the TEP in the dark is corneal-positive. For example, if $V_{ap} = -90$ mV and $V_{ba} = -75$ mV, the TEP will be $V_{ba} - V_{ap}$ or +15 mV. The TEP is a major component of the standing potential of the eye.

During the c-wave, the TEP increases (becomes more positive). This could occur either because the apical membrane becomes more negative (hyperpolarizes) or because the basal membrane becomes less negative (depolarizes). Intracellular RPE recordings from both intact and in vitro preparations[48] show that the RPE c-wave is generated by a hyperpolarization of the RPE apical membrane.

The amplitude of the RPE c-wave, however, is not equal to the apical hyperpolarization because some of the apical voltage is passively shunted to the basal membrane (the two membranes are only partially separated). This basal voltage subtracts from the apical voltage and makes the recorded TEP smaller. Thus, the amplitude of the RPE c-wave depends on the responses of both the apical and basal membranes. Recent experiments (and theoretical predictions) show, for example, that a decrease in basal membrane resistance (see the later section on interactions between distal ERG components) decreases the passive basal response and therefore increases the RPE (and corneal) c-wave.

Recordings with double-barreled K^+-selective microelectrodes where one barrel measures intraretinal voltages and the other measures potassium concentration show that the RPE c-wave and the apical hyperpolarization have a time course similar to the light-evoked, subretinal $[K^+]_o$ decrease.[37, 38] The apical membrane has a large relative potassium conductance.[31] In the frog, Oakley[37] compared light-evoked responses from a retina-RPE preparation with K^+-evoked responses from an isolated RPE preparation (where only K^+ in the apical bathing solution was altered). He was able to show that the RPE c-wave was due solely to the $[K^+]_o$ decrease. Recent experiments using Ba^{2+} and ouabain show that a decrease in $[K^+]_o$, in addition to increasing the potassium equilibrium potential and hyperpolarizing the apical membrane, also slows the electrogenic apical Na^+ $-K^+$ pump[32] and produces a small apical depolarization.[14] This indicates that at

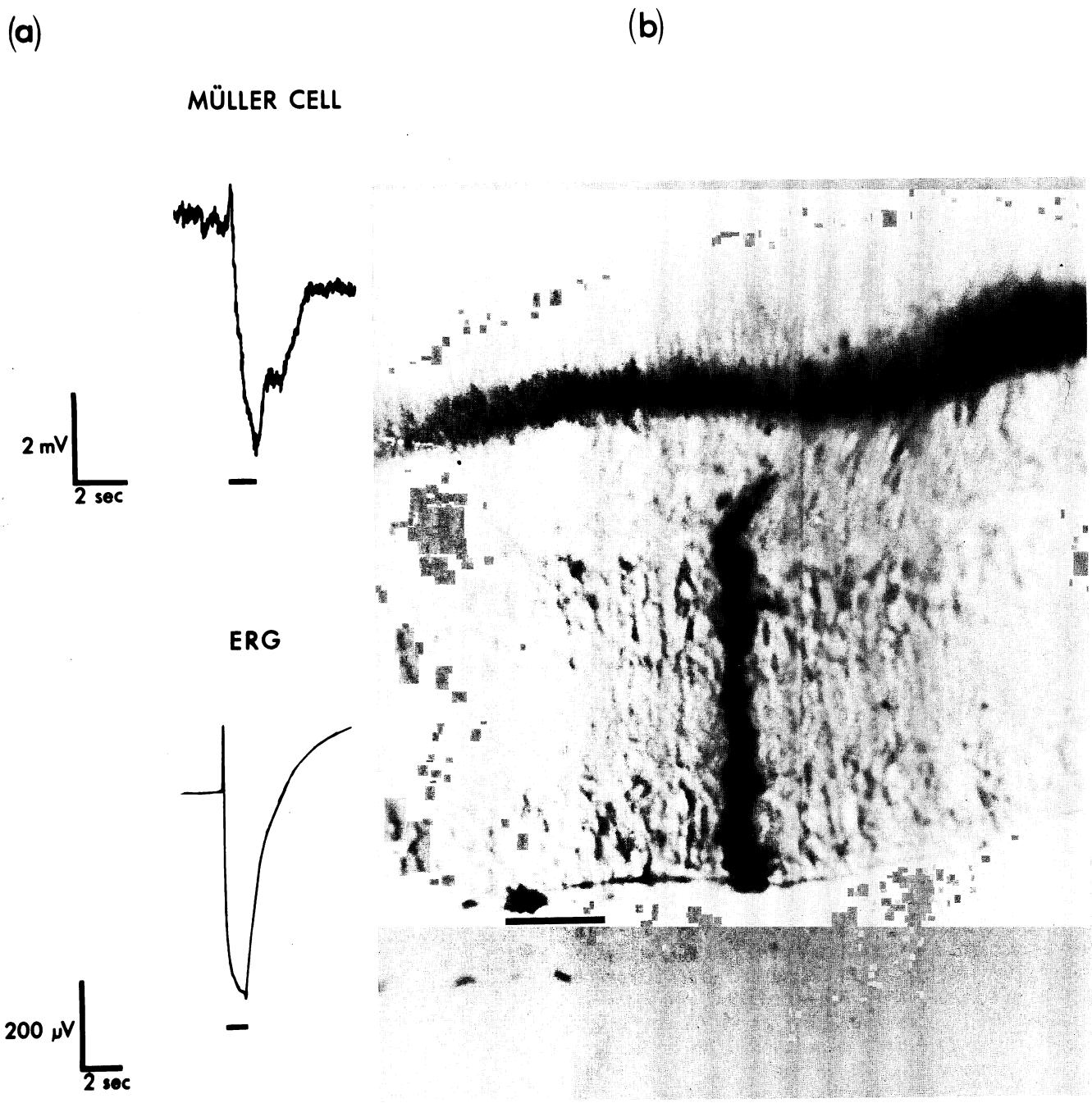

FIG 9–3.
Origin of slow PIII. **A,** intracellularly recorded Müller cell response *(upper trace)* and simultaneously recorded ERG *(lower trace)* from a superfused rabbit eyecup. The duration of the diffuse white light stimulus is indicated by the *horizontal bars.* The light response consists of a transient depolarization followed by a sustained hyperpolarization. The ERG shows a positive b-wave followed by a sustained negative PIII component. **B,** The HRP-stained Müller cell from which the intracellular recording in **A** was obtained (calibration bar; 25 μm). (From Dick E, Miller RF, Bloomfield S: *Gen Physiol* 1985; 85:911–931. Used by permission.)

least two apical mechanisms contribute to the RPE c-wave.

Findings presented above show that the c-wave reflects responses of both Müller and RPE cells to a light-evoked $[K^+]_o$ decrease. Since the amplitude of the vitreal c-wave is the difference between these two components, a change in the $[K^+]_o$ response should alter both components, and the c-wave amplitude may change little. On the other hand, if only one of the components were altered, the percent change in the amplitude of the vitreal c-wave will be greater than the percent change in that component.[46]

With longer periods of illumination, subretinal K^+ starts to reaccumulate, and this causes both the RPE c-wave and slow PIII to recover from their peaks. In the frog, the time course of this recovery is quite similar to the K^+ reaccumulation.[39] In response to maintained illumination, $[K^+]_o$ fell to a minimum value and then began to recover, reaching a steady state approximately 10 minutes after light onset. In the frog, the TEP of the RPE TEP followed $[K^+]_o$ during this entire time period, whereas in other species, the recovery toward the dark-adapted baseline is greater than predicted by the K^+ reaccumulation (see below).

THE FAST-OSCILLATION TROUGH

The fast-oscillation trough (usually measured by EOG; see Chapter 39) is a change in the corneoretinal potential—decreasing in light and increasing in dark in synchrony with an oscillating light/dark stimulus. In this section we examine the responses evoked by maintained illumination that correspond to the EOG decrease (trough). This decrease in potential, termed the fast-oscillation trough,[51] follows the c-wave peak (Fig 9–4,B). If a light peak is also evoked by the stimulus (see the next section), the fast-oscillation trough appears as a dip between the c-wave and the light peak (see Fig 9–2).

The fast-oscillation trough has subcomponents

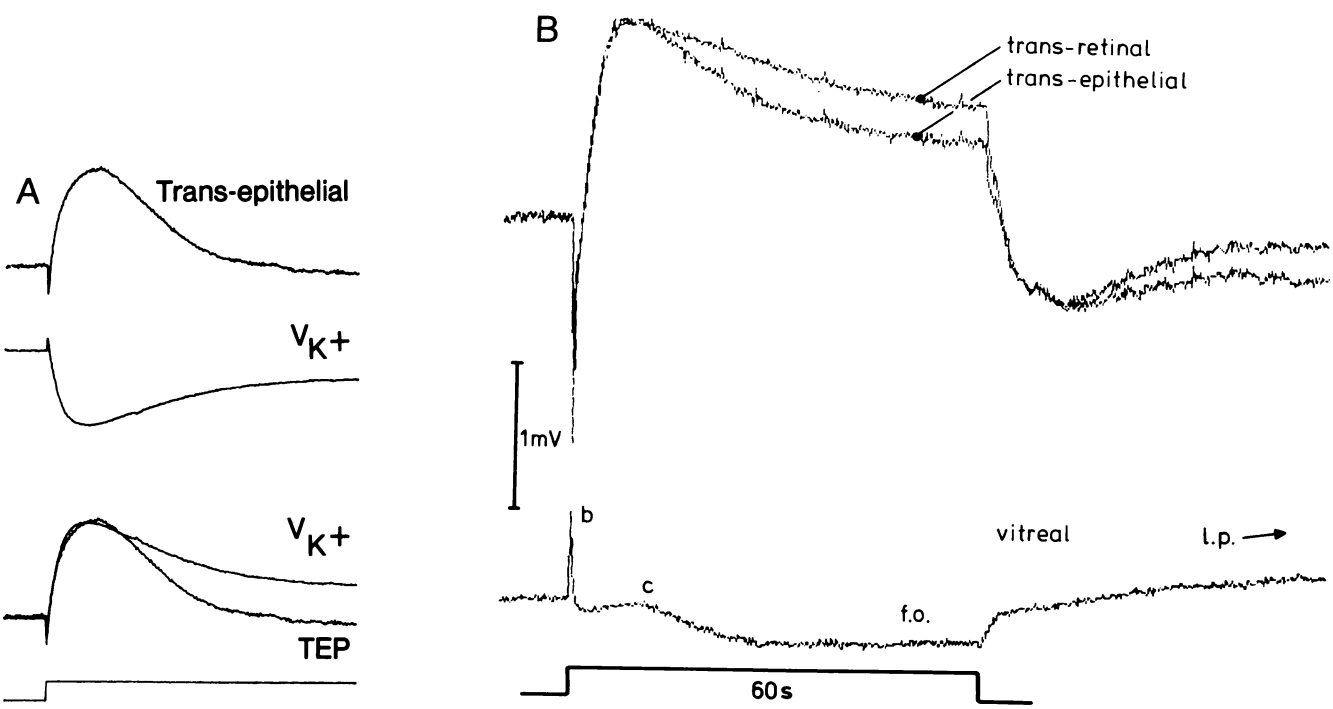

FIG 9–4.
Intraretinal recordings during the fast-oscillation trough. **A,** simultaneous recordings of the TEP and the potassium change (V_K) in an in vitro gecko retina-RPE-choroid preparation in response to a 3-minute period of white light illumination. The potassium response has been inverted and scaled to the peak of the TEP recording so that the two recordings can be compared. The TEP decrease from its peak is greater than predicted by the change in V_K. (Adapted from Griff ER, Steinberg RH: *Gen Physiol* 1984; 83:193–211.) **B,** simultaneous recordings of the vitreal, transretinal, and transepithelial potentials in the macaque in response to a 60-second stimulus. The transretinal potential was inverted and superimposed on the transepithelial recording. The TEP decreases from its peak more than the transretinal potential does. It was coincidental that both recordings had equal amplitudes. Since the vitreal ERG is the sum of the two subcomponent voltages, the vitreal c-wave is very small in this example. (From van Norren D, Heynen H: *Vision Res* 1986; 26:569–575. Used by permission.)

that originate in both the neural retina and the RPE. One subcomponent involves the recovery of Müller and RPE cells from their peak polarizations as $[K^+]_o$ reaccumulates. However, in many species, including mammals, birds, and reptiles, the recovery of both slow PIII and the RPE c-wave from their peaks is greater than predicted by the reaccumulation of subretinal $[K^+]_o$ (Fig 9–4,A). The deviation is greatest for the RPE component such that it recovers more toward the dark-adapted level than does slow PIII (Fig 9–4,B). As discussed by Steinberg et al.,[46] this extra decrease in TEP produces much of the corneal-negative potential during the fast-oscillation trough.

Intracellular RPE recordings in cat, gecko, chick, and bovine RPE show that this extra TEP decrease is generated by a hyperpolarization that originates at the RPE basal membrane. This basal hyperpolarization is passively shunted to the apical membrane where it overrides the apically generated depolarization that should occur as $[K^+]_o$ reaccumulates. Thus, light produces, first, a hyperpolarization generated at the apical membrane that *increases* the TEP and, second, a hyperpolarization generated at the basal membrane that *decreases* TEP. Since the basal hyperpolarization follows the apical hyperpolarization, it has been called delayed basal hyperpolarization.[15]

The mechanism underlying delayed basal hyperpolarization has been studied in isolated RPE preparations of the gecko, chick, and cow. In these species, a maintained decrease in $[K^+]_o$ in the apical bath first hyperpolarizes the apical membrane so that the TEP increases (analogous to the RPE c-wave) and subsequently hyperpolarizes the basal membrane so that the TEP decreases back toward the baseline. In these experiments, the only "stimulus" is a step decrease in $[K^+]_o$ with no reaccumulation. These experiments suggest that the light-evoked $[K^+]_o$ decrease in the subretinal space of an intact retina is sufficient to produce both the c-wave and the fast-oscillation trough.

The ionic mechanisms as well as the intracellular steps of this basal response are currently under investigation.[12] It is not known whether basal hyperpolarization results from passive ionic changes or from modulations of an electrogenic pump. Furthermore, although delayed basal hyperpolarization is accompanied by an apparent decrease in basal membrane conductance, it is not known whether this conductance change causes or results from the basal hyperpolarization. Experiments in frog RPE show that spatial buffering across the RPE can decrease $[K^+]_o$ in the subchoroidal space (an unstirred layer between the basal membrane and the choroidal vessels) when subretinal $[K^+]_o$ decreases.[18] This subchoroidal $[K^+]_o$ decrease also could produce the delayed basal hyperpolarization.

THE LIGHT PEAK

In mammals, birds, and reptiles, maintained illumination causes a slow increase in the standing potential that is called the *light peak*,[20] and this can also be recorded as a slow oscillation of the EOG (see Chapter 39). Intraretinal recordings in the cat,[27] monkey,[50] chick,[11] and gecko[16] show that this corneal positive potential comes exclusively from the RPE as an increase in the TEP (see Fig 9–2). Intracellular RPE recordings show that the TEP increase is generated by a slow depolarization of the RPE basal membrane and is accompanied by an apparent increase in basal membrane conductance. It is not known whether this conductance increase during the light peak causes or results from the slow basal depolarization.

Although the light peak voltage comes from the RPE, an initial event occurs in the neural retina that in turn triggers a change in the concentration of an as yet unidentified "light peak substance." Since the light peak persists following treatments to block synaptic transmission to postreceptor cells,[11] photoreceptor activity alone probably modulates the concentration of the light peak substance. The sensitivity of the light peak to hypoxic levels that do not affect the ERG b-wave[22] also suggests a photoreceptor origin. While both experimental and clinical studies have suggested that the inner retina may also contribute,[13, 21, 28] the perturbations used in these studies could also have affected the photoreceptors and/or RPE directly.

The RPE mechanisms underlying the light peak voltage are also unknown. Recent experiments have shown that treatments that depolarize the RPE basal membrane, thereby decreasing its resistance, suppress the light peak. This has been shown in the intact cat eye for hypoxia and azide,[26, 27] in the perfused cat eye for both dopamine and dibutyl cyclic adenosine monophosphate (cAMP)[5] and in an in vitro chick preparation for hyperosmolarity and dopamine.[42, 45] A dopamine antagonist, *cis*-flupenthixol, depressed the light peak in the perfused cat eye.[5] Both dopamine and cAMP are modulated by light,[1, 10] but there is not sufficient evidence to identify either as the light peak substance. 4,4′-Diisothiocyanostilbene-2,2′-disulfonate (DIDS), an anion transport inhibitor, blocks both the light

peak and the depolarizing effects of dopamine in the chick.[12] The effects of DIDS suggest that the light peak may originate as an increase in a basal membrane anion conductance. The effects of dopamine on this basal anion conductance are being investigated.

INTERACTIONS BETWEEN DISTAL ELECTRORETINOGRAPHIC COMPONENTS

The amplitude of the c-wave undergoes significant variation during the rise and fall of the light peak.[23] When repetitive flashes that elicit both c-waves and a light peak are used, intraretinal recordings have shown that the increase in the c-wave during the light peak originates from the RPE component. Intracellular recordings reveal that the RPE c-wave increases as a result of a decrease in the resistance of the RPE basal membrane. A similar increase in c-wave amplitude has also been observed with systemic mild hypoxia[22, 33, 44] and intravenous azide injections,[26, 35] both of which also decrease RPE basal membrane resistance. It would not be surprising to find a similar effect in diseases that affect the RPE.

Nikara et al.[34] described an ERG wave in the cat that he called the second c-wave. This consists of a shoulder on the rising phase of the light peak (see Fig 9–2). Detailed analysis of the subcomponents arising in the neural retina and RPE show that this shoulder probably does not represent a discrete subcomponent.[24] Rather, it results from the interaction between the end of the delayed basal hyperpolarization, the initiation of the light peak, and the maintained K^+-dependent hyperpolarization of the apical membrane.

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