Principles and Practice of Clinical Electrophysiology of Vision

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The Scotopic Threshold Response

Laura J. Frishman

A negative response near threshold in the dark-adapted electroretinogram (ERG) has been observed in humans[4, 15, 18] and in several animals including cats,[8, 17] monkeys,[21] sheep,[10] and toads.[7] This negative response at stimulus onset dominates the dark-adapted diffuse flash ERG of the cat at intensities of 3.1 to 4.6 log q $deg^{-2}s^{-1}$. It grows in amplitude for the first 1.5 log units of intensity, and then a positive-going potential, the (dc) component of PII, emerges. At higher intensities (e.g., 7.6 log q $deg^{-2}s^{-1}$ in Fig 11–6), the b-wave dominates the response. The negative response to dim stimuli was initially termed the scotopic threshold response (STR) in the cat because of its sensitivity demonstrated in intraretinal recordings (see below).[17] The STR is distinct from the scotopic a-wave, although it resembles the a-wave at some intensities (e.g., the arrow at 5.6 in Fig 11–6). Aspartate, which isolates photoreceptor responses,[20] removes the STR, and this indicates that it originates proximal to the photoreceptors.[22] The scotopic a-wave, which emerges in the ERG only at relatively high intensities, survives the asparate treatment. The STR may have a lower threshold than the a-wave because the gain of responses can be increased substantially at synapses proximal to photoreceptors.[1]

THE STR AS A SEPARATE RESPONSE

Intraretinal analysis in the cat shows that the negative potential in the dark-adapted ERG elicited by dim stimuli originates in the proximal retina.[17] The proximal response is negative going for the duration of the stimulus when brief stimuli of durations <300 ms are used (Fig 15–1) and returns slowly to baseline at light off. For longer stimulus durations (not shown), after the initial 300 ms the response arches toward baseline during illumination and reaches a plateau around 2.5 seconds after stimulus onset.[5] The STR can be distinguished both from the M-wave of the proximal retina and from PII of more distal retina in the cat. It differs from the M-wave in several respects: (1) the STR is a rod rather than a cone-dominated response, (2) it generally lacks the separate off response of the M-wave, and (3) it sums over a large retinal area and does not show the selectivity for small spots that is characteristic of the M-wave.[16, 17] Sieving et al.[17] showed that the STR differs from PII with respect to depth distribution, stimulus-response characteristics, and the relative strength and polarity of contributions to the ERG. These findings are described below.

Depth Distribution

Responses recorded in the dark-adapted retina at increasing retinal depths to very dim stimulus spots or diffuse stimuli are clearly maximal in the proximal retina (17% retinal depth) around the border between the ganglion cell and inner plexiform layer.[17] In contrast, PII (dc component and b-wave) is maximal near 50% retinal depth around the inner nuclear layer (INL), as is well documented.[3] If the stimulus is so weak that PII is not elicited, the STR can be seen to reverse polarity in midretina (Fig 15–1, 50% depth) and thus is a positive-going signal in the distal retina. This reversal suggests a source proximal to and a sink distal to the reversal point, and in confirmation, current source density analysis shows

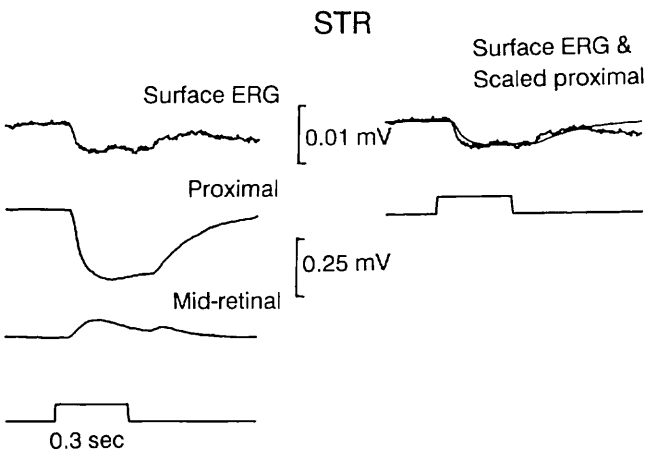

FIG 15–1.
The STR dominates intraretinal recordings and the ERG at low stimulus intensities below the threshold for PII. On the *left*, the *top* trace is the surface ERG recorded about 25μm from the retinal surface, and the *bottom* two traces are recordings of the STR in the proximal retina (about 6% retinal depth) and the inverted STR around 50% retinal depth. On the *right*, the scaled STR recorded in the proximal retina is superimposed on the surface ERG to show the similarity of the responses. For the surface ERG, a microelectrode was referenced to a wire in the vitreous in order to reduce the effects of stray light.[2] This minimized contributions to the ERG of retinal regions distant from the recording site of the intraretinal signals (spot size, 9.9 degrees; spot illumination, 4.8 log q $deg^{-2}s^{-1}$). (Adapted from Sieving PA, Frishman LJ, Steinberg RH: *J Neurophysiol* 1986; 56:1049–1061.)

source and sink activity in the midretina.[19] At higher stimulus intensities, the reversed signal in the midretina and distal retina is replaced by PII.

Intensity

The plot in Figure 15–2 shows peak amplitudes, as a function of intensity, of the negative responses in the proximal retina where the STR was maximal and in the midretina where PII was maximal. The plot shows that the first measurable response for the STR (filled symbols) is about 1.5 log units lower than the first measurable response for PII (open symbols), in the same four cats. The STR appears at a lower intensity than PII, and it also saturates at a lower intensity: around 5.8 log q $deg^{-2}s^{-1}$ in the plot, about 2.4 log units lower than saturation of the rod b-wave in the cat.

Contribution to the ERG

The similarity of the onset times of the proximal retinal STR and the negative potential in the cat ERG

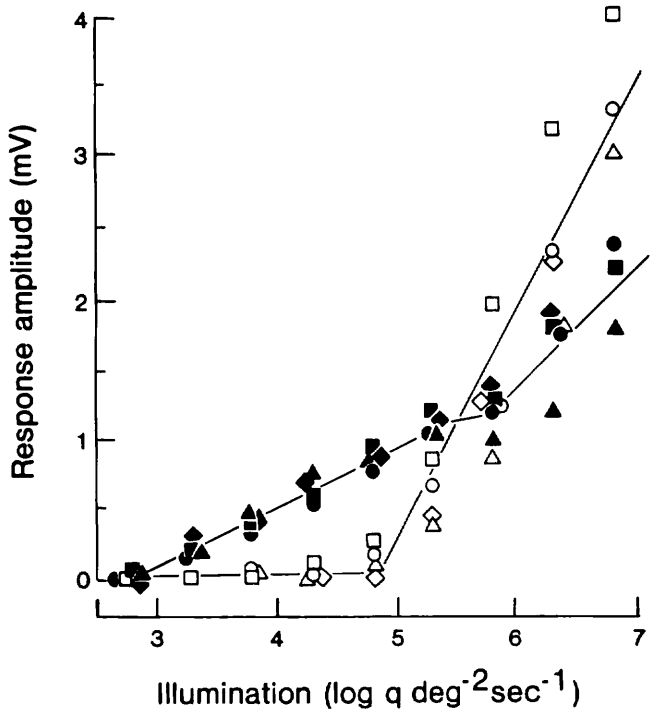

FIG 15–2.
Amplitudes of dark-adapted responses in the proximal retina *(filled symbols)* and in the midretina *(open symbols)* as a function of stimulus illumination. Measurements were made in the proximal retinas of four cats where the STR was maximal and in the midretinas of the same four cats where PII was maximal. In the midretina, measurements were made from negative-going responses only, and they were made at the peak of the responses, which means that the dc component of PII was measured at low intensities and the b-wave was measured at high intensities. (From Sieving PA, Frishman LJ, Steinberg RH: *J Neurophysiol* 1986; 56:1049–1061. Used by permission.)

supports the idea that the STR contributes the vitreal negative potential to the ERG that dominates at threshold and at very low intensities. Furthermore, Sieving et al.[17] found that they could match the threshold negative response in the ERG, off-line on the computer, by scaling the STR from proximal retina at its recorded negative polarity. This is shown in Figure 15–1. At higher stimulus intensities, when PII was recorded in the midretina, PII dominated the ERG (not shown).

A K^+–MÜLLER CELL MECHANISM FOR THE SCOTOPIC THRESHOLD RESPONSE

Frishman and Steinberg[6] examined the hypothesis that the STR, in analogy to the M-wave in am-

phibia, is associated with Müller cell responses to $[K^+]_o$ released by proximal retinal neurons by measuring light-dependent changes in $[K^+]_o$. They identified a light-evoked increase in $[K^+]_o$ in the proximal retina of a dark-adapted cat that had obvious behavioral similarities to the STR: the dynamic range from threshold to saturation of the increase in $[K^+]_o$ in the proximal retina was similar to that of the field potentials (Fig 15–3), and the retinal depth maxima for the light-evoked increases in $[K^+]_o$ coincided with that of the STR field potentials. It was not possible to determine whether the latency and rise time of the $[K^+]_o$ increase exactly matched that of the STR since measurements were limited by the rise time of the K^+ electrode. Therefore the possibility cannot be eliminated that an initial portion of the proximal field potential in a dark-adapted retina is neuronal in origin, by analogy to the PNR. On the other hand, the $[K^+]_o$ increase in the proximal retina was more sustained than were the field potentials in the proximal retina, and the ERG contained a slow negative response that matched the duration of the $[K^+]_o$ increase.

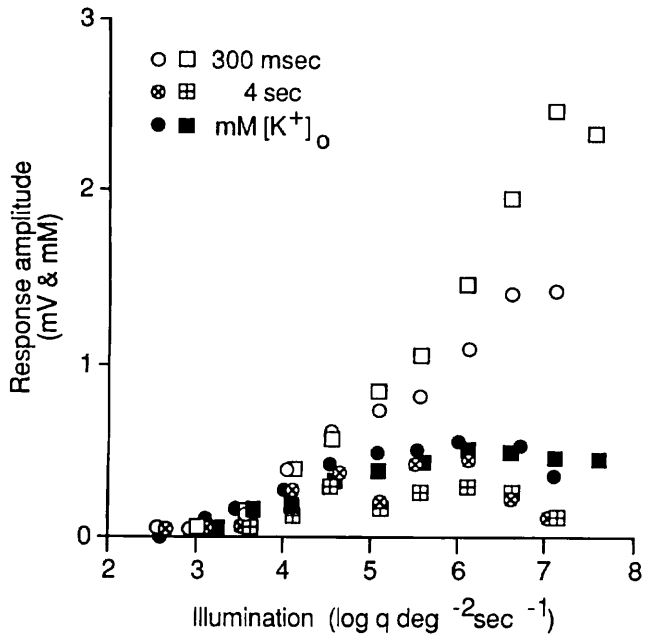

FIG 15–3.
Amplitude of dark-adapted responses in the proximal retina and the light-evoked increase in $[K^+]_o$. Measurements were made with double-barreled K^+-sensitive microelectrodes in the proximal retina where the STR was maximal. The plot includes amplitudes of the proximal responses at 300 ms after stimulus onset *(open symbols)* and 4.0 seconds after stimulus onset *(crossed symbols)*. $[K^+]_o$ was measured at the peak of the response. Measurements were made in two cats. (From Frishman LJ, Steinberg RH: *J Neurophysiol* 1989; 61:1233–1243. Used by permission.)

A causative role for the $[K^+]_o$ increase in creating the negative potentials, presumably via K^+ currents in Müller cells, was supported by the finding that Ba^{2+}, a K^+ conductance blocker, eliminated the proximal field potential in the cat and the negative potentials in the ERG but did not, initially, eliminate the light-evoked increase in $[K^+]_o$ in the proximal retina.[6] In amphibian Müller cells, Newman and Odette[14] modeled the b-wave so that current flow was virtually all toward the vitreal endfoot where K^+-conductance is highest.[12] The polarity of the b-wave supports this model: it is negative going throughout the retina, and positive going in the vitreous. The direction of current flow for the STR must be different since the STR is negative going in the vitreous and proximal retina and it inverts in the midretina. This suggests a strong K^+ current toward the distal retina in the cat Müller cell. The distribution of K^+ conductivity in the cat Müller cell is consistent with a relatively strong distally directed current since the cat Müller cell has high conductances at both ends, with the distal end higher than the proximal end.[11]

There is good evidence in amphibia that Müller cells buffer extracellular $[K^+]_o$ changes in the retina by siphoning K^+ from one region to another.[9, 13] In the cat, Frishman and Steinberg[6] observed a spread of the proximal retinal $[K^+]_o$ increase seen near threshold into the distal retina. Whereas the proximal increase was present after Ba^{2+} treatment, the distal $[K^+]_o$ increase was eliminated, which supports the idea that the K^+ released in the proximal retina in the cat was carried to the distal retina via the Müller cell.[6]

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