Principles and Practice of Clinical Electrophysiology of Vision

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46

Scotopic Threshold Response of the Electroretinogram

Paul A. Sieving

A NEGATIVE ELECTRORETINOGRAPHIC RESPONSE NEAR ROD THRESHOLD

A very dim light evokes a small, corneal-negative wave in the electroretinogram (ERG) of a fully dark adapted human eye. This response was first called the scotopic threshold response (STR) in the cat ERG by Sieving et al.[32] In the human ERG intensity series of Figure 46–1, the STR occurs with stimuli too dim to elicit the b-wave (i.e., PII, which includes the dc component with dim stimuli and the b-wave with brighter stimuli) or the a-wave (fast PIII from the photoreceptors). Thus the STR can be recorded without interference from other ERG components that are seen only with brighter stimuli. The psychophysical scotopic threshold was near 1.4 log quanta (507)/degree^2 for the subject in Figure 46–1.

An STR has been identified in the ERG of human,[1a, 33] monkey,[35, 38] cat,[32] and dog.[6] Similar threshold negative responses can also be found in the ERG literature previous to 1986 (see below).

HISTORY OF THE SCOTOPIC THRESHOLD RESPONSE

Among the earliest observations of a negative component in the human ERG for dim light was that by Schweitzer and Troelstra,[29] who a negative wave near the PII threshold. Schweitzer and Padmos[28] subsequently separated this negative component further and reported a separate ERG wave of small amplitude at 150-ms latency for stimuli 1 log unit above the human absolute psychophysical threshold; they could not determine whether or not this was the late receptor potential. Arden and Brown[2] recorded the ERG of the cat with intraretinal microelectrodes and described a "surround negativity" with very dim lights for the special condition of an annular stimulus, although they could not identify its origins. Finkelstein and associates[11] showed a negative wave in the human ERG for stimuli within 0.7 log units of the absolute (psychophysical) threshold and suggested this wave was part of PIII activity from the distal retina. Knave et al.[20] saw a slow, negative, transient component in the ERG of sheep beginning 2.5 log units below the b-wave threshold, but their analysis suggested that this was the rod receptor potential. Jacobson and Ikeda[15] noted for the cat that both the threshold response and the b-wave disappeared after experimental retinal arteriolar occlusion, and they concluded that the origin of this activity was postphotoreceptoral.

Recent evidence that the threshold ERG originates in the proximal retina comes from microelecrode recordings at various depths in the cat retina by Sieving et al.[32] ERG activity for the dimmest stimuli occurred in the inner plexiform and inner nuclear layers, not near the photoreceptors that generate the a-wave. STR activity was also more proximal in the retina than PII, which is recorded deeper in the retina and only with stimuli several log units brighter than required for the STR.

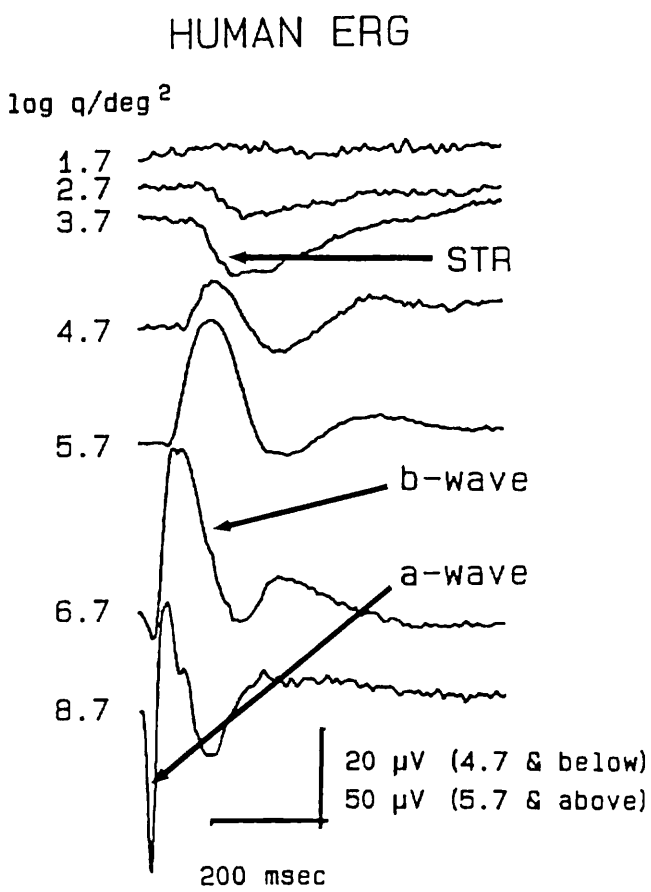

FIG 46–1.
Human ERG intensity series for a 10-ms flash in a Ganzfeld bowl and recorded with a corneal electrode. A corneal-negative STR wave is seen with very dim stimuli. The b-wave (PII) is present at 4.7 log q/deg^2 and above. The a-wave (fast PIII) is present by 6.7 log q/deg^2 and above. Note the scale change between 4.7 and 5.7 log q/deg}. The absolute psychophysical threshold for this subject was at 1.4 log q/deg^2. The flash occurred at the start of these traces.

CHARACTERISTICS OF THE SCOTOPIC THRESHOLD RESPONSE

The STR is a graded, negative wave in the corneal or intraretinal ERG. The maximum amplitude is about 20 μV at the cornea, but it can reach several hundred μV when recorded by a microelectrode in the proximal retina. The STR is driven primarily by stimulus onset, and very little or no separate activity is noted at stimulus cessation. The STR is elicited best with large or diffuse stimuli.[32] While averaging techniques are helpful in studying the fine details of the STR, the wave can also be observed without averaging, even from humans (Fig 46–2).

With intraretinal recordings in the cat, the minimum stimulus intensity to record an STR is at or

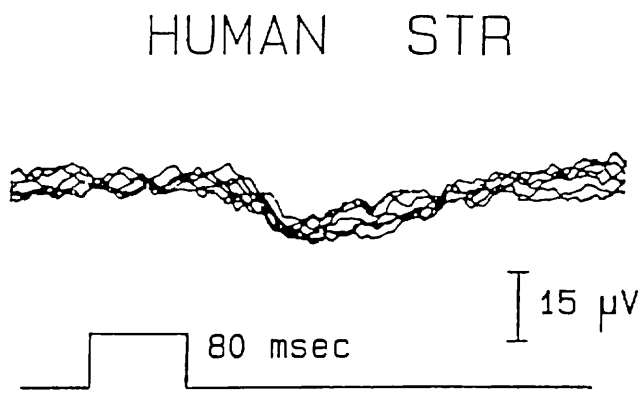

FIG 46–2.
Threshold ERG negative response photographed directly from a storage oscilloscope screen from a human subject with very dim stimuli below threshold for the b-wave. The STR is clearly evident even without averaging responses.

very near visual threshold by comparison with ganglion cell sensitivity.[32] For human corneal ERG recordings, the STR threshold lies within 0.7 log units above the psychophysical threshold.[11, 33] The V-log I curve for the STR (Fig 46–3) is nearly linear at dim

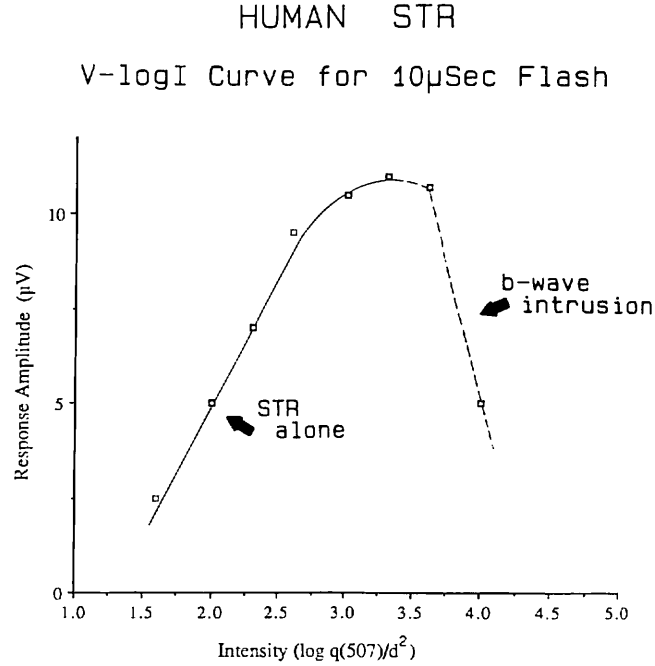

FIG 46–3.
V-log I curve of the human STR. The STR amplitude increases linearly with log stimulus intensity and begins to saturate near the threshold to observe the b-wave. Above 3.0 to 3.5 log q/deg^2 the apparent STR amplitude is deminished by the b-wave. (From Sieving PA, Nino C: *Invest Ophthalmol Vis Sci* 1988; 29:1608–1614. Used by permission.)

intensities and saturates about 2.5–3 log units above threshold for cat and human[32, 33] (Sieving, Frishman and Steinberg, 1986b; Sieving and Nino, 1988) which is near the intensity at which PII first dominates.

For the dimmest stimuli the negative deflection of the STR wave begins at a latency of nearly 190 ms after stimulus onset for 80-ms flashes and decreases to about 100 to 110 ms near the b-wave threshold (Fig 46–4). The STR latencies are considerably faster for very brief stimuli and range from about 140 down to 90 to 100 ms for 10-μs xenon flashes. The dependence of STR latency on flash duration results from the temporal integration properties of the response. The latency–log I function of the STR is nearly linear for both long (Fig 46–4) and short flashes.

The temporal properties of the human STR were studied with stimuli of short and long durations.[33] The critical stimulus duration for the STR amplitude was at least 80 ms. Quanta presented during the initial 80 ms (but not out to 165 ms) contributed to the peak amplitude: the STR amplitude for 8-ms stimuli at 5.3 log q(507)/deg^2 sec was identical to the amplitude for 80 ms flashes at 4.3 log q(507)deg^2 sec. Thus the STR followed Bloch's law for at least 80 ms, comparable to what was also measured for psychophysical summation at visual threshold for the same human subjects.

Since the STR is elicited by very dim stimuli, it could be presumed to be rod driven. Rod univariance for the STR was demonstrated by using red and blue stimuli that were matched for the scotopic luminosity function of humans,[33] cats, and mon-

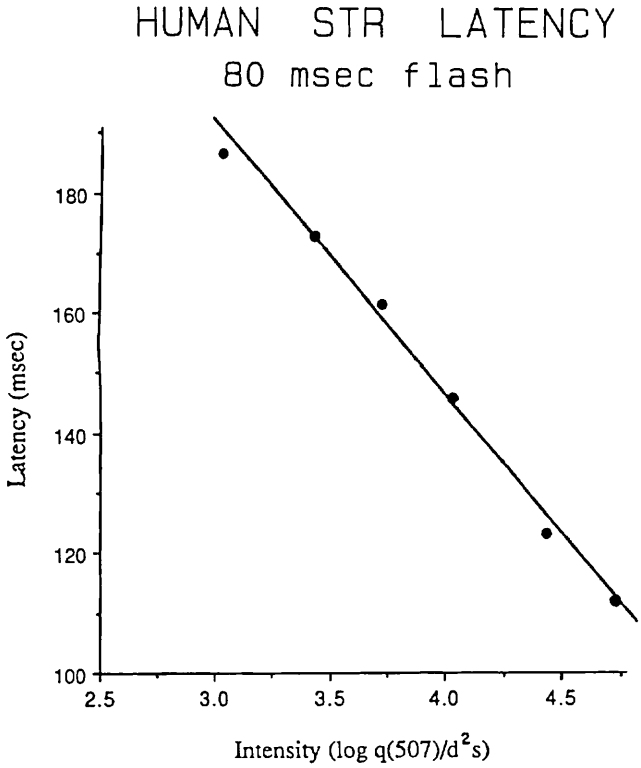

FIG 46–4.
The latency of the human STR decreases linearly with log stimulus intensity. These responses were elicited by 80-ms stimuli, which give long STR latencies due to the long critical duration of the STR (up to about 100 ms). STR latencies are considerably shorter for 10-μs flashes and range from 140 ms at threshold to 90 to 100 ms near the b-wave threshold. (From Sieving PA, Nino C: *Invest Ophthalmol Vis Sci* 1988; 29:1608–1614. Used by permission.)

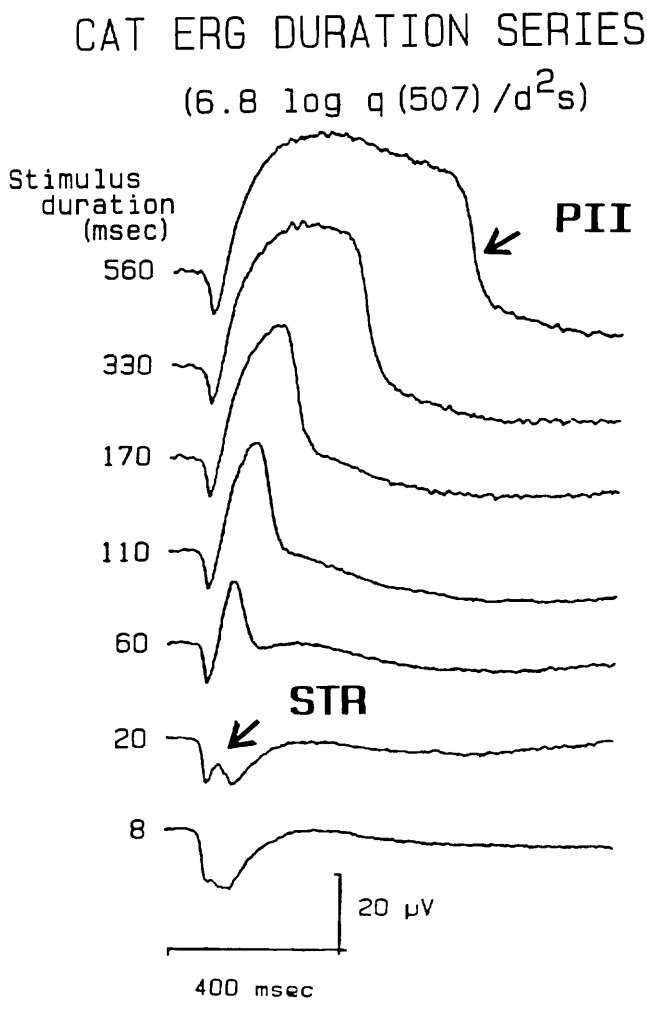

FIG 46–5.
ERG duration series at a single intensity for the cat. The negative STR wave is present throughout but is seen best with shorter stimuli. With longer stimuli the dc component of PII is observed as the sustained response of positive polarity that obscures the later portion of the STR. Shorter stimuli help to isolate the STR from PII.

keys.[39] The STR waveform was identical in amplitude, latency, and morphology for these two rod-matched stimuli.

SCOTOPIC THRESHOLD RESPONSE WAVEFORM INTERACTION WITH PII (dc COMPONENT AND b-WAVE)

The STR is readily distinguished from PII in the corneal ERG waveform polarity since the STR is corneal-negative while both the dc component and b-wave are corneal-positive. With intraretinal recordings, both the STR and PII are predominantly negative potentials,[32] but they can be separated by retinal depth since the STR maximum amplitude lies more proximal in the retina than does PII.

At the cornea the STR can be recorded in relative isolation from PII by taking advantage of stimulus intensity since the STR is seen with stimuli that are too dim to elicit PII (see Figs 46–1 and 46–3). The STR is essentially the only component in the corneal ERG for stimuli up to 2.5 log units above the psychophysical threshold. Above 3 log units above the psychophysical threshold, PII progressively obscures the STR. Short flashes are also helpful in separating the STR from PII, as shown in Figure 46–5. Since PII is a sustained waveform for dim flashes (i.e., the dc component), longer stimuli favor PII, whereas short stimuli favor the STR (Fig 46–5). In clinical STR recordings, we use flashes of 10 μs, 10 ms, and 100 ms to identify the human STR.

COMPARISON OF THE SCOTOPIC THRESHOLD RESPONSE BETWEEN SPECIES

In order to identify the value of studying the STR in subhuman species, we compared the cat, monkey, and human ERG recorded with the same 80-ms stimulus in the same Ganzfeld stimulator.[39] The

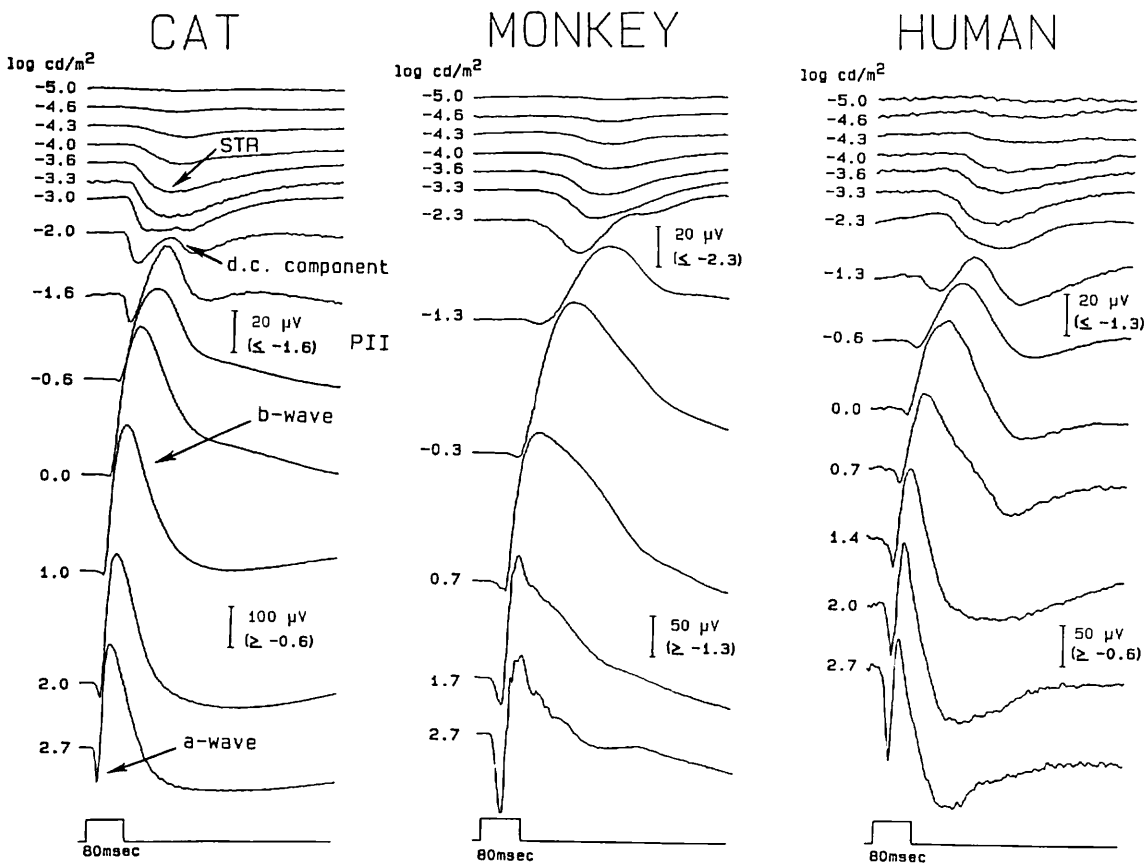

FIG 46–6.
ERG intensity series for the cat, monkey, and human, recorded with the same Ganzfeld stimulus at 80 ms. All three species show similar ERG components at comparable stimulus intensities. The single difference is the faster latency of the STR and b-wave of the cat as compared with the monkey and human. (From Sieving PA, Wakabayashi K: *Clin Vis Sci*, 1990, in press. Used by permission.)

characteristics of the STR were remarkably similar for the cat, monkey, and human in waveform, intensity range, and amplitude (Fig 46–6). Only the STR latency was different for the cat (75 ms near threshold) as compared with monkeys and humans (180 ms near threshold). Since the latencies of the rod b-wave and the rod visual evoked response (VER) were also faster for the cat than for the monkey and human,[35] we suggested that the propagation of rod visual signals through the retina may be faster for the cat and that it did not indicate fundamentally different origins or mechanisms of the STR in these species. Thus the predominantly rod retina of the cat appears to be suitable to study the STR and is helpful for understanding the human STR.

Surprisingly, our preliminary studies of the rabbit ERG showed that the threshold component was corneal-positive rather than a corneal-negative STR as in the cat, monkey, and human. We tested only New Zealand white rabbits and do not know whether other varieties have a negative STR. The difference between the threshold ERG of the rabbit and of the cat, monkey, and human may stem from different distributions of Müller cell potassium conductances for different species.[35]

RETINAL ORIGINS OF THE SCOTOPIC THRESHOLD RESPONSE

The STR is not a field potential from the photoreceptors. Although the STR is a negative ERG component at the cornea, like the a-wave that results directly from photoreceptor activity,[26] intraretinal recordings of the STR implicated the STR origin in the proximal retina.[32] The depth profile of the STR in the cat retina, in Figure 46–7, shows a vitreal-negative dipole that extends into the inner plexiform layer. Maximal activity lies in the proximal retina, and minimal or no STR activity is evident near the photoreceptors in Figure 46–7. Further evidence against a photoreceptor origin of the STR comes from injecting monosodium aspartate into the vitreous of the cat and monkey eye.[38] Aspartate suppressed the STR and PII but spared fast PIII (a-wave), as shown in Figure 46–8. This result demonstrated that the STR originated postsynaptic to the photoreceptors.

A current source density (CSD) analysis of the intraretinal STR of the cat also indicated a proximal retinal origin, with a source and sink positioned in the region of the inner plexiform and inner nuclear layers,[36] consistent with amacrine cell involvement

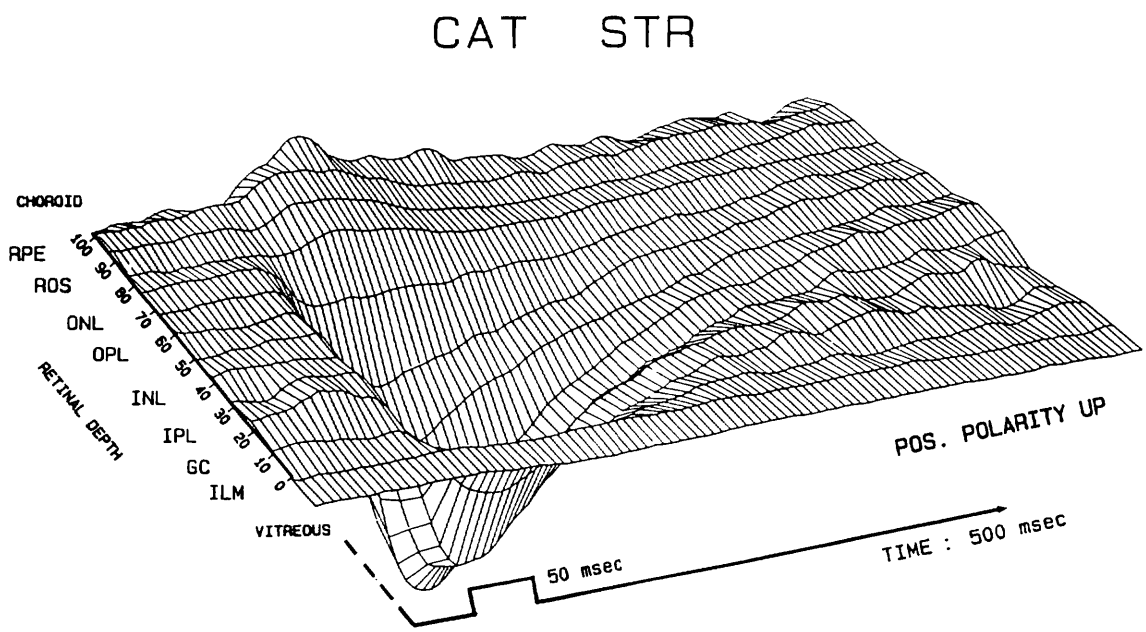

FIG 46–7.
Intraretinal recordings of the STR of the cat at various retinal depths. Positive polarity is up, and the reference electrode is in the anterior vitreous just behind the lens. For this dim stimulus (4.0 log q(507)/deg^2 sec), the main intraretinal activity occurs in the proximal retina, with the maximum STR at 20% to 35% retinal depth in the inner plexiform layer *(IPL)*. The STR dipole is vitreal-negative, and a very tiny negative STR wave is recorded at the surface of the retina in the vitreous. Since little or no contribution comes from the photoreceptors *(ROS)*, these intraretinal studies show that the STR is different from the a-wave (RPE = retinal pigment epithelium; ONL = outer nuclear layer; OPL = outer plexiform layer; INL = inner nuclear layer; GC = ganglion cell; ILM = inner limiting membrane).

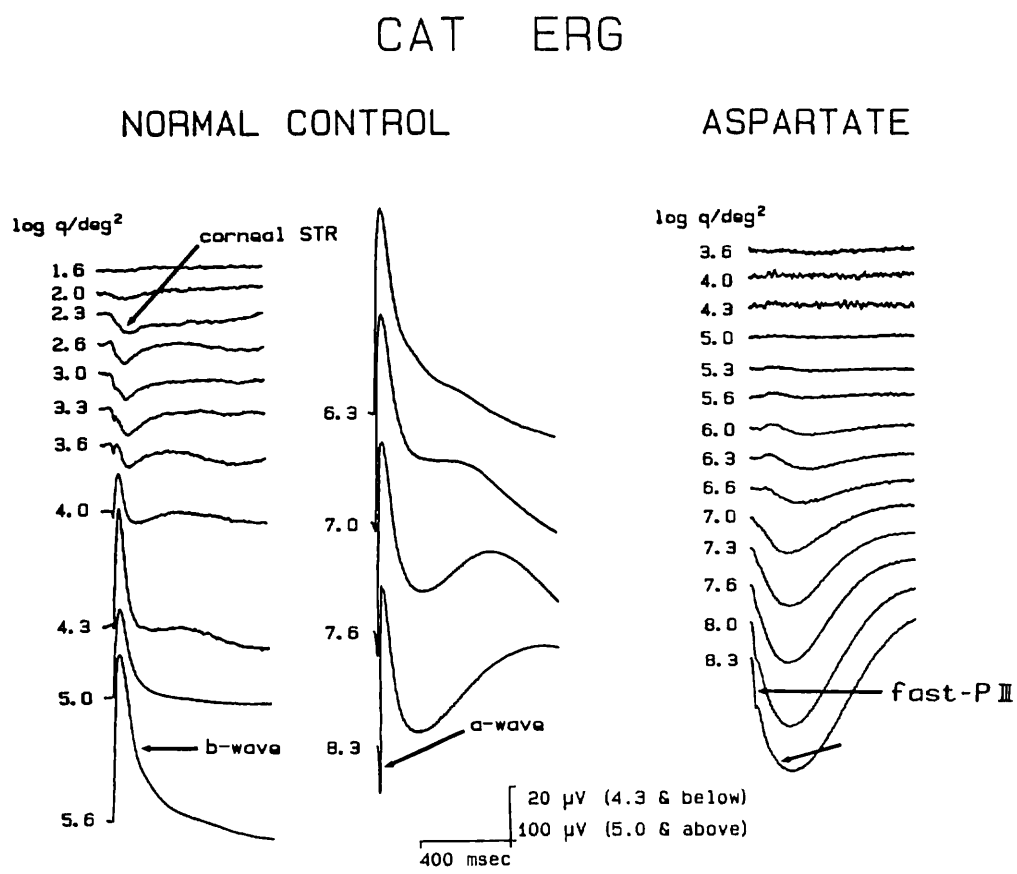

FIG 46–8.

ERG intensity series before and after monosodium aspartate (130 μM total dose) injected into the vitreous of the cat. Aspartate abolished the STR and suppressed the PII (b-wave) responses, but it did not affect fast PIII (a-wave) from the photoreceptors. This indicated that both the STR and PII originate postsynaptic to the photoreceptors and that the STR is different from the a-wave. (Adapted from Wakabayashi K, Gieser J, Sieving PA: *Invest Ophthalmol Vis Sci* 1988; 29:1615–1622.)

in the STR production, although ganglion and bipolar cells could not be absolutely excluded by this approach.

Ganglion cells were eliminated as the primary origin of the STR by experimental, unilateral optic nerve section of the cat.[30] When the ERG was recorded up to 21 months later, the STR was still present with nearly normal amplitude despite a loss of the nerve fiber layer and of all ganglion cells on histological examination of sections of the experimental retina. A similar preservation of the human STR was found for a subject who had complete, unilateral optic atrophy from a fracture of the left optic foramen 22 years previously that had not disturbed retinal vascular perfusion.[30]

The current hypothesis is that the STR derives from a potassium–Müller cell mechanism in the proximal retina.[12, 13] A light-evoked increase in extracellular potassium concentration is recorded in the proximal retina under stimulus conditions that evoke only an STR and with a retinal depth distribution that resembles the STR.[13] Ba^{2+}, which blocks K^+ conductance of Müller cells, eliminated the STR.[13, 14] The potassium release in the proximal retina might come from amacrine cells, as is believed underlie M-wave generation under photopic conditions.[17]

Intraretinal potassium studies also provided evidence that the STR is different from slow PIII: there was no potassium decrease in the subretinal space at very dim intensities and therefore no slow PIII or c-wave.[14] The elimination of the STR but not slow PIII by 2-amino-4-phosphonobutyric acid (APB) further distinguished these components as having different origins.[14]

PHARMACOLOGY OF THE SCOTOPIC THRESHOLD RESPONSE

Pharmacological studies of the STR to date have concentrated on neurotransmitter and neuromodula-

tor agonists and antagonists known to be active in the proximal retina of the cat and monkey. Both γ-aminobutyric acid (GABA) and glycine suppressed the STR completely and reversibly.[24] Strychnine blocked suppression of the STR by glycine. Strychnine alone enhanced the STR amplitude slightly but reliably. The suppression of the STR by GABA was partially antagonized by bicuculline and by picrotoxin.

While both glycine and GABA suppress the STR, they have different effects on PII of the cat: glycine slightly decreased the amplitude of PII, but GABA increased PII near its threshold. Since the STR and PII were affected independently, these pharmacological studies suggested that the STR origin was different from that of the rod PII, which is presumed to involve the depolarizing bipolar cells.

An as yet unexplained observation is the greater sensitivity of the STR as compared with PII for small doses of aspartate injected into the vitreous of the cat.[38] A trivial explanation is that the origin of the STR lies more proximal in the retina than PII and that the intravitreal aspartate diffused first to the depth of the STR before diffusing deeper to reach PII generators. More interesting, however, is the possibility that aspartate affected n-methyl-D-aspartate (NMDA) receptors in the proximal retina somewhat independently or at lower concentration than effects on PII generators in more distal retina. Karwoski and Proenza[18] had reported an effect of aspartate on proximal retinal function under light-adapted conditions; here the M-wave of the proximal retina and the proximal negative response (presumed amacrine cell activity[8]) were reduced more than PII, which could even be enhanced.

PHYSIOLOGY OF THE SCOTOPIC THRESHOLD RESPONSE

Quantal Sensitivity of the Scotopic Threshold Response

The STR is recorded in the first 3 log units above the absolute visual threshold after prolonged dark adaptation. This equates to intensities of less than 1 quantum per rod. Microelectrode recordings in the proximal retina of the cat yield an STR threshold near 2.7 log q(507)/d^{2}sec, which is 1 quantum per 560 rods (assuming an integration time of 80 ms), comparable to the most sensitive of cat ganglion cells (−2 log q(507/μm^{2}sec).[5] Limitations of diffuse stimuli and signal-to-noise degradation of corneal ERG recordings limit identifying the human STR to 0.7 log units above the absolute human visual threshold,[33] equivalent to 1 quantum per 245 to 490 rods for Ganzfeld stimuli. By comparison, the b-wave is first observed when every rod receives about 1 quantum on average.

Rod Pathway in Starlight

The question of whether and at what light level the STR saturates is important since the rod system does not inherently saturate at 3 log units above visual threshold. The operative range of rod-PII continues well above the STR range, and rod saturation (near 3 log td for humans[1] and 2.5 log td for cats[27]) occurs 2.5 to 3 log units above STR saturation. One intriguing explanation is that the STR may reflect the activity of a specific neural pathway through the inner retina, called the rod bipolar pathway for very dim scotopic signals: rods → rod bipolar → AII amacrine → CBb1 → ganglion cell.[37] It may also be of importance that scotopic visual signals must pass through amacrine cells to reach the ganglion cells to exit the eye.

Retinal Gain

How is it that the STR is for recorded stimulus intensities several log units below the a-wave and b-wave? The STR is recorded at intensities of 1 quantum shared among 10 to 1,000 rods. The hyperpolarization of a rod in response to a single quantum is quite small and will escape notice in gross extracellular potentials of the ERG unless many rods are stimulated simultaneously. Further, electrical coupling between photoreceptors is believed to dampen membrane noise fluctuations,[22] and (we can speculate) this might suppress the a-wave field potential when only a single rod is stimulated.

Neural amplification through the retinal layers helps to explain the STR appearance at low intensities. The synaptic connections between rods and bipolar cells exhibit a severalfold gain, estimated as high as 50 for the dogfish retina.[3] Further gain occurs at synapses onto amacrine cells.[21] Thus for threshold stimuli, the activity of the inner retina is proportionately greater and presumably can be recorded and identified in the ERG. A second type of amplification of threshold signals is provided by the divergence of the rod pathway through successive retinal layers: one rod synapses onto two or more bipolars and, in turn, onto yet more AII amacrine cells.[37] Since stimuli for the STR intensity range are substantially less than 1 quantum per rod, this di-

vergence will recruit proportionately more cells in each successive retinal layer proximal to the photoreceptors, and the resultant ERG activity of the proximal retina will be enhanced.

Scotopic Vision Lacks Spatial Sensitivity

The STR is best elicited with large or diffuse stimuli, and it does not show spatial tuning.[32, 41] This absence of spatial sensitivity of the STR reflects the properties of rod-driven signals in the proximal retina in which the antagonistic surround of cat ganglion cells is desensitized after prolonged dark adaptation.[4, 10] By comparison, many cone-driven responses are stimulated best by small spots of light and can show spatial tuning, such as the proximal negative response,[8] the M-wave,[17, 31] and the pattern ERG.[23, 34]

TIPS FOR RECORDING THE HUMAN SCOTOPIC THRESHOLD RESPONSE FROM CLINICAL PATIENTS

We record the STR routinely from untrained but cooperative human subjects after dark adapting for about 1 hour (Fig 46–9). We amplify signals by 10,000 gain and record for 300 or 500 ms to accommodate the long latency of the human STR. Averaging about 15 responses provides adequate signal-to-noise enhancement. Blink artifact rejection is critical for recording these small responses. A rejection window of 100 μV is appropriate since this will not truncate legitimate STR responses. Several records at each stimulus intensity allow us to judge the reliability of the small STR wave. With this strategy we are able to identify STR responses of 1 to 2 μV quite reliably.

Suitable electrodes include DTL fibers (Dawson, Trick, Litzkow),[9] which we have used for up to 6 hours per session without difficulty. For recording from clinical patients, we use the Burian-Allen bipolar contact lens electrode (Hansen Ophthalmic Development Laboratory, Iowa City, Iowa), which can be inserted in the dark after dark adaptation.

Appropriate amplification to record the STR will depend on the recording system. The human STR amplitude is about 20 μV maximum at the cornea, and the typical noise for 20 averages is about 0.25 to 0.5 μV. Our system has 12-bit resolution (4,096 steps) and a 10-V range, which gives 2.5 mV per digital step (10 V/4,096 steps). With a preamplifier gain of 10,000, the final resolution is 0.25 μV per digital step, which provides good signal-to-noise resolution for the STR. Digitizing systems that use only 8 bits (256 digital steps) will require greater preamplification to achieve comparable resolution.

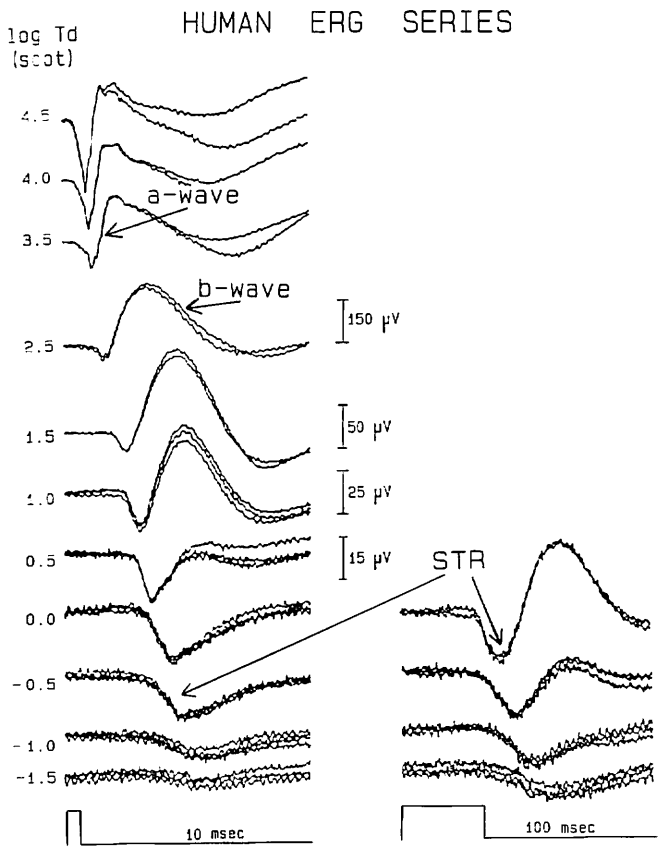

FIG 46–9.
ERG intensity series from a clinical patient with a Burian-Allen bipolar electrode and 300-ms recording. This subject was not "trained" for ERG recordings but rather came for clinical diagnosis. Reliability is judged by recording multiple responses at each intensity. Using two stimulus durations allows observing the temporal integration properties of the STR and PII.

The STR frequency range is about 0.5 to 50 Hz. We use a band-pass filter, with 3-dB attenuation at 0.1 and 300 Hz. However, recording at 1 to 100 Hz is also suitable and has several advantages: a 1-Hz lower limit minimizes saturation and blocking of the preamplifier at 10,000 gain due to blinking; a 1-Hz limit does not alter the waveform peak amplitude since the low-frequency components are only in the tail of the STR (as it returns slowly to baseline).

Stimulus intensities to record the STR are about −5.0 to −1.0 log scotopic cd/m^2 surface luminance for a Ganzfeld bowl for the cat, monkey, and human.[39] For a human with a fully dilated pupil of 9 to

10 mm, the STR is readily seen between −1.5 and +1.0 log scotopic trolands (Td) for 10-ms stimuli (see Fig 46–9). The b-wave threshold lies near 0.5 log scotopic Td for 10-ms flashes (see Fig 46–9). The conversion to trolands is Td = cd/m^2 × pupil area (mm).

Control of stimulus duration is helpful in separating the STR from PII responses near PII threshold, for identifying response features elicited by light onset from those elicited at light off, and to explore the temporal properties of the ERG components. We typically use 10- and 100-ms stimuli presented in a Ganzfeld bowl with light from a tungsten-halogen lamp that is shuttered for the required durations. As shown in Figure 46–9, comparable STR and PII responses are seen at −0.5 log Td for 100-ms flashes and for +0.5 log Td for 10-ms flashes, thus demonstrating the reciprocity of intensity and time with these stimuli. When elicited by 10-μs xenon flashes, the STR latency will be appreciably faster than for longer stimuli due to the temporal integration property of the STR.

CLINICAL APPLICATIONS OF THE SCOTOPIC THRESHOLD RESPONSE

In our clinical recordings to date, all normal subjects have an STR. As seen in Figure 46–10, we have found some patients with an abnormally small STR even though the b-wave appears at the normal threshold (0.5 log scotopic Td for 10-ms flashes in Fig 46–10) and the b-wave maximum is within normal range. These patients have had poor peripheral and central vision but lacked clear diagnoses.

The STR provides a new clinical avenue to explore the rod pathway through the inner retina in "starlight." Since the STR appears to be more sensitive than the rod b-wave to ischemia of the inner retina,[15, 38] the STR may have clinical value in following diabetic microangiopathy[1a] that affect the cone oscillatory potentials of the inner retina.[7, 40] However, much remains to be learned about the possible clinical value of the STR.

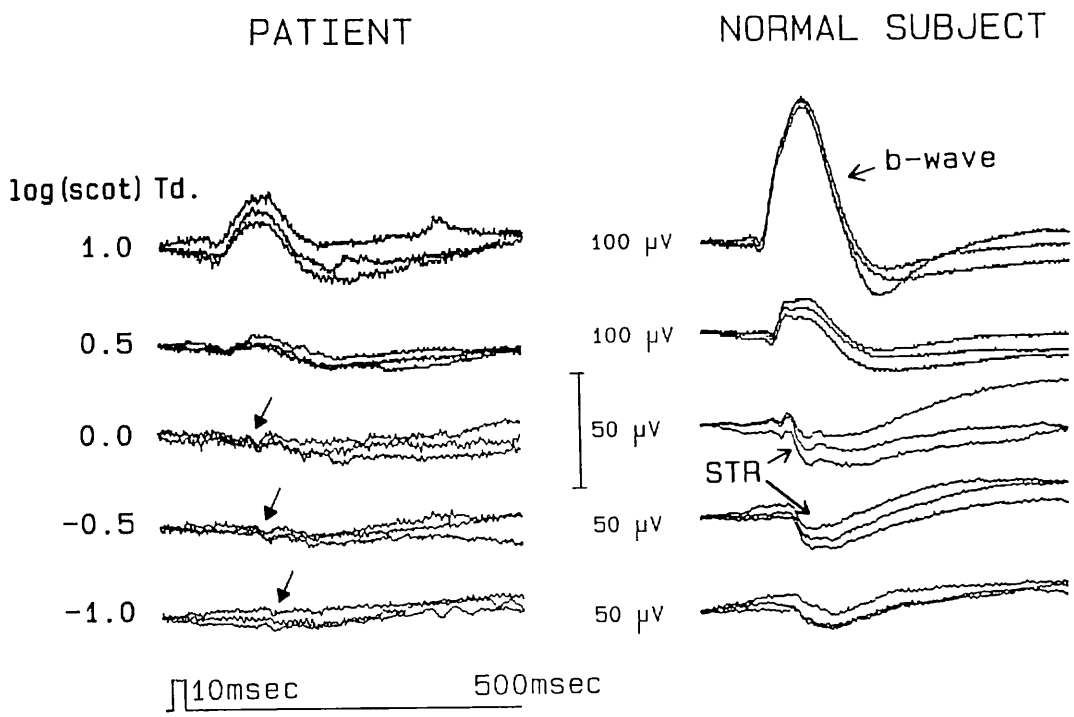

FIG 46–10.
STR responses from a patient with vision loss and elevated intraocular pressure. The patient had an enlarged cup-disc ratio, but vision loss was not thought to be solely from glaucoma. Although the patient's STR was greatly reduced in amplitude, it was demonstrated reliably by the tiny negative deflection at the appropriate latency and was highly reproducible in these recordings and on repeat 2 months later. The patient's b-wave V-log I curve was shifted to 0.5 log units higher intensity, with low-normal maximum amplitude. Both have b-wave thresholds near 0.5 log scotopic Td (for 10-ms flashes). Burian-Allen bipolar electrodes (10-ms stimulus, 500-ms recording duration, 15 averages) were used.

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