Principles and Practice of Clinical Electrophysiology of Vision

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PART VIII

Other Protocols for Recording of Electroretinographic and Slower Potentials

40

Early Receptor Potential: Origin and Clinical Applications

William W. Dawson
Nicholas R. Galloway

Brown and Murakami[7] recorded a complex photolabile response from a microelectrode placed in the receptor layer of the monkey retina. The latency of the response was hard to measure but was very short (<0.1 ms). Later work with resolution of 10 microseconds or better has not reported a measurable latency. Brown and Murakami called this the early receptor potential (ERP). The ERP has been recorded from a number of species, many containing largely rods[8] or largely cones.[17] Arden et al.[1] conclude that the early, positive portion of the ERP, called R_1, is a direct result of the first photochemical events whereas the following, negative portion, called R_2, is generated within the surface membrane as a change in the array of fixed charges. Soon after the report of Brown and Murakami, Yonemura and Kawasaki[28] recorded a potential with similar time properties from intact human eyes. Recent reviews have been provided by Müller and Töpke[15] and van Norren.[26]

NATURE AND ORIGIN OF THE EARLY RECEPTOR POTENTIAL

Work on vertebrates has shown that the two components R_1 and R_2 can be separated by low temperature. The R_1 component persists in the rat down to a temperature of −35°C, whereas the R_2 component is eliminated at 0°C.[17] The ERP disappears above a temperature of 50°C, a level that is high enough to disorganize the outer segments.[9] The source of the ERP survives in the absence of sodium ions and also immersion in formalin. These findings together with the very short latency of the response have been taken to indicate that it results from displacement of charge in illuminated visual pigment molecules.[5] Further evidence for this is supplied by the fact that the amplitude of the ERP is linearly related to stimulus energy.[8] This is in contrast with the later components of the ERG, which tend to show a logarithmic relation to stimulus intensity. Another important feature of the response is the way in which it is influenced by dark and light adaptation. Immediately after one bright flash the response is diminished due solely to the bleaching of visual pigment. This photolability distinguishes the response from electrical artifacts and also the melanin potential.

The ERP may be recorded from most eyes by using technology similar to that for routine electroretinograms (ERGs). It can be recorded from the isolated eye for hours after death.[8] However, special requirements are imposed if quality recordings of an unequivocal nature are to be obtained. These special requirements arise from the large amounts of light needed to produce the ERP and the remarkably rapid temporal properties of the ERP itself. In the older literature, photoflash lamps with very high energy inputs (100 J or more) were used as stimulators. Since most of the ERP is complete by 1 ms after the flash begins, the need for a light with a very rapid rise time is clear. Flash lamps were the obvious choice. However, these are associated with relatively high (5 to 10 kV) trigger (ionizing) potentials. The

voltage and speed of the trigger potential results in a troublesome artifact from which the eye electrodes and preamplifier must be shielded. The trigger artifact rise time is measured in microseconds and is quite similar to the R_1 portion of the ERP. Since the peak of R_1 (e.g., Fig 40–1) occurs at about 88 microseconds (or earlier), the amplifier and recording system must have a very wide bandwidth if all components of the ERP and subsequent late receptor potential are reproduced faithfully. The records in Figure 40–1 were obtained with an amplifier whose band pass (3-dB points) was 1 Hz to 125 kHz. The recording device was a computer with a high-speed digitizer that provided 10-microsecond resolution. Many workers use an oscilloscope and recording camera.

The ratio of the amplitude of R_1/R_2 varies from 1:4 to 1:20 depending on the reporting clinic; the strength of the stimulus has not yet been standardized. The amplitudes vary depending on the strength of the flash and its distance from the eye. Walther and Hellner measured $R_1 + R_2$ in 180 normal eyes by using a 145-J flash and obtained a mean amplitude of 163 μV.[27] Zanen[29] has used an averaging technique to record the ERP. By this means he has shown that a response as small as 0.3 μV can be detected. It has been estimated that a response of 140 μV in a dark-adapted eye is the equivalent of a 20% pigment bleach whereas a response of 0.3 μV is equivalent to a 1% pigment bleach.[29]

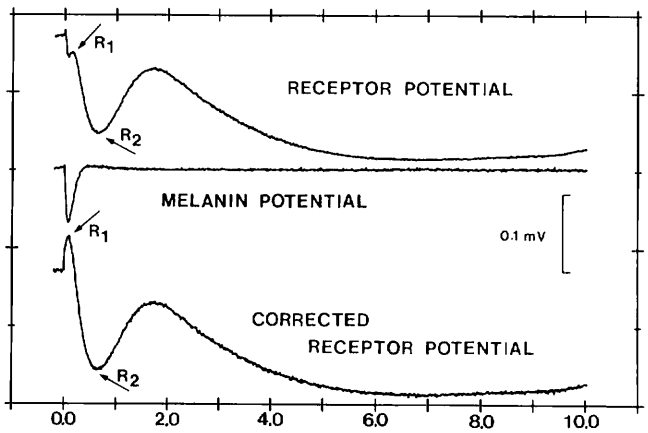

FIG 40–1.
Early and late receptor potentials recorded from a 12-day-old Rhode Island Red chicken under anesthesia after adaptation to −2 log footlamberts (fL). Lamp input was 21 J (280 fL·sec at the cornea). The flash rise time was 5 microseconds. The melanin potential remained at 30 minutes postmortem and after 5 minutes of bleaching at 4 log fL. The digitized (10 microseconds) melanin potential was subtracted from the receptor potential to produce a corrected receptor potential. R_1 and R_2 are the ERP components. The late receptor potential begins at 2 milliseconds. The flash was delivered at 0 microseconds.

THE EFFECT OF LIGHT ADAPTATION ON THE NORMAL RESPONSE

After a single response, a further immediate stimulus may fail to produce a detectable response because there is insufficient unbleached pigment remaining in the outer segments. The amplitude of the ERP is related to the quantity of unbleached pigment present in the eye.

Modern short-arc xenon flash lamps can efficiently stimulate an ERP by confining the majority of the output energy to the area of the eye rather than producing diffuse-unusable energy common to the wide dispersion angles in photographic flash units. Figure 40–1 was produced by a 21-J lamp input, 3-mm arc gap EG&G (EG&G Electro-Optics & Electronic Components, Salem, Mass.) short-arc lamp. The 3-mm arc was collected with a parabolic reflector and condenser lens system and imaged upon a half-inch fiber optic bundle. The bundle passed through a shield wall into the recording chamber where there was a second lens that produced approximately a 5-mm-diameter illuminated area in the plane of the cornea. With this arrangement, less input energy was dissipated, and rise times and decay times of the light flash were shorter. Usable ERP R_2 signals could be produced by this flash system with input energies less than 0.5 J. For lamp inputs from 0.5 to 21 J, stimulus intensities at the cornea measured in foot-lambert-seconds (fl · sec) ranged from 10 to 280.

Electrodes are the other major concern in ERP recording. There must be a relatively low interelectrode impedance (3-5 kΩ or less at 1000 Hz for effective common-mode rejection) and no exposed wires or other materials that can produce photovoltaic artifacts in response to the high light levels. Bare metal electrodes such as used in some contact lenses are the most objectionable type. Carefully light shielded, "wick-style", fluid-filled electrodes are commonly used. The potentials in Figure 40–1 were recorded from a stainless steel electrode inside a wick electrode tube filled with a jellied electrolyte (electroencephalographic [EEG] paste). The wick (black cotton) electrode tube was carefully light shielded with black vinyl tape. While this arrange-

ment is suitable for animal research under anesthesia, it is obviously improper for human use because of corneal discomfort. Sieving et al.[20] used a saline-filled cotton wick electrode for human subjects. Walther and Hellner[28] describe an elegantly shielded, artifact-free (in the presence of 145 J), fluid-filled contact lens (similar to the Henkes' electrode) that provides a maxwellian view. Reference electrodes must also be carefully shielded from the stimulating light and, for best electrical artifact rejection, should be placed as close as possible to the cornea.

Biological pigments can add to the artifact problem. Brown and Crawford[6] found a fast photovoltage excited by intense light in the pigment epithelium. Ebrey and Cone[10] concluded that this potential was a direct response of the melanin itself. If the photolabile pigment of the retina is eliminated, the melanin potential can be recorded. In Figure 40–1 the receptor potential is shown in an intact eye with both photolabile and photostable pigments present. After the animal was euthanized and photolabile pigments heavily bleached, the melanin potential was recorded as the midpotential in Figure 40–1. Since these data were digitized, it was possible to subtract the melanin potential from the receptor potential. This produced a corrected receptor potential where R_1 may be seen accurately. Under conditions of balance between the melanin potential and R_1 (which have about the same time properties) we have seen recordings in which it appeared that there was no R_1 present. Apparently because of this problem, some authors use R_2 alone for quantitative results. This practice may be undesirable in cases where cone abnormality is suspected. Goldstein and Berson,[11] Tamai and Holland,[22] and Sieving and Fishman[18] have commented on selective R_1 loss in human monochromats.

In mammals, the ERP is highly biased toward cone receptors. This makes it potentially of great value in the clinic and in research specifically involving cones and the early events in color vision. Clinical use is well under way, and normative data from humans have been reviewed.[16] There is a growing list of clinical reports identifying a few conditions that have been evaluated by ERP: macular neuroretinopathy,[21] siderosis,[19] retinitis pigmentosa,[14] and color defect.[24] The most expanded clinical study may be the one by Walther and Hellner.[27] Their first norm group had an ERP amplitude standard deviation of 30%. This was reduced to 18% in a second group when more care was given to stimulus delivery. They have demonstrated that most diseases of the posterior pole have effects upon ERP amplitude or timing. Changes of time course (retinitis pigmentosa) or selective amplitude changes (monochromatism) tend to encourage further experimentation. The ERP is an important retinal signal when quantitative information on receptor outer segment function is needed.

THE EFFECT OF DISEASE ON THE EARLY RECEPTOR POTENTIAL

Color Blindness

Spectral response curves have been plotted in a series of protan and deutan subjects and compared with normal individuals. When log ratios of R_2 amplitude at 460 and 600 nm are compared in the different groups, significant differences are seen.[25] Similar differences in the responses of deuteranopes and protanopes have been shown by using a slightly different technique and measuring $R_1 + R_2$ amplitudes.[23] In a rod monochromat, the early receptor potential was 40% of its normal value and showed a half-life of five to six minutes. The reason for this very prolonged recovery is not clear in this case, but it is suggested that it may be related to the rather marked nystagmus that was present.[11]

Cone Dystrophies

Although the ERP as recorded in the clinic appears to have a strong cone component, it has been disappointing to find that cone-specific disease does not seem to have much influence on the response.[27] However, a more recent study of seven patients with an autosomal dominant cone dystrophy seems to suggest that changes in the ERP can be observed. In this series the mean amplitudes of the ERP to red, green, and blue flashes was much reduced in the patients with cone dystrophy as compared with normal controls.

Retinitis Pigmentosa

An investigation of the ERP in this condition reveals that it is reduced in amplitude but may still be present at a late stage of the disease. Measurement of the recovery time reveals that this is faster than normal. It has been suggested that this abnormally rapid recovery may be due to disappearance of the more slowly recovering rod response or perhaps to a more generalized abnormality of receptor function.[3] It has also been claimed that similar changes may be found in carriers.[4] A study of the ERP in a series of

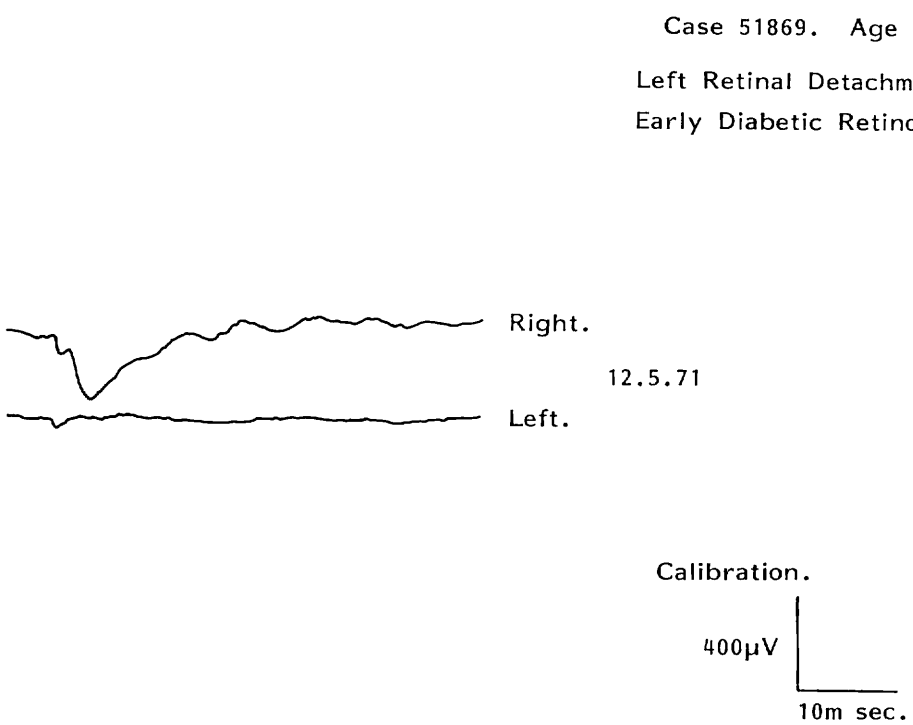

FIG 40–2.
The bright flash response in a diabetic patient who developed a detached retina in one eye. The ERP is still present in the eye with the detachment, but the rest of the ERG is abolished.

rats with an inherited retinal dystrophy has shown that the response is larger than normal in the diseased rats in the early stage of the disease. After this initially augmented response, the amplitude became reduced and eventually disappeared after 60 days. This finding seemed to parallel a previously described initial increase in the content of rhodopsin in the outer segments.[2]

Other Disease of the Retina and Optic Nerve

As might be expected, the ERP has been recorded as normal in the presence of optic atrophy.[12, 13] It has also been recorded as normal in the presence of an occlusion of the central retinal vein, although it is reduced after central retinal artery occlusion. The response is markedly reduced although not abolished in the presence of a retinal detachment (Fig 40–2). In patients with ocular siderosis the ERP has been shown to be relatively well preserved when compared with the rest of the electroretinogram. This suggests that the receptors may be well preserved, at least in the early stages of the condition.[19]

In spite of the accumulation of information concerning the clinical application of the ERP, many more data are still needed before its real value can be fully assessed.

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