THE EARLY RECEPTOR POTENTIAL IN THE HUMAN ELECTRORETINOGRAM

Daizo Yonemura and Kazuo Kawasaki

Department of Ophthalmology, School of Medicine
Kanazawa University, Kanazawa, Japan

The early receptor potential (ERP) of the retina was found by Brown and Murakami (1964a, b) in the monkey. The ERP has been reported to exist in some other animals and to be closely linked with the initial events of visual excitation (Cone, 1964, 1965; Pak and Cone, 1964; Pak and Ebrey, 1965; Brown, 1965; Brown, Watanabe and Murakami, 1965; Pak, 1965; Arden and Ikeda, 1965, 1966; Brindley and Gardner-Medwin, 1966). It seems of special interest to know whether or not a similar response is present in the human retina. The purpose of this paper is to describe a new rapid potential with a very short latency (less than 30 µsec) in the human electroretinogram (ERG) and to infer the retinal portion responsible for the generation of this new potential. Some of our findings have been reported in preliminary form (Yonemura, Kawasaki and Hasui, 1966; Kawasaki, 1966).

METHODS

The stimulus flash was provided by a 100-W-sec xenon discharge lamp through which a capacitor of 250 µF charged to 900 V was discharged. The flash was effectively dissipated in 0.8 msec, the peak luminance occurring after 0.3 msec. The flash light was led to the eye through a fibre optics bundle 50 cm in length and 6 mm in diameter. One end of this bundle was placed close to the flash lamp. The other end was located 3 mm from the cornea. The filters which excluded wavelengths shorter than 350 mµ and longer than 800 mµ were placed in the light path. The interval between stimulus flashes was 5 minutes.

The electrodes consisted of saline-soaked black cotton wicks leading to platinum wires. Except for the tip, each electrode was wrapped with black tape. With these precautions, the stimulus artefact was reduced to a minute potential having a duration of less than 30 µsec. The tip of the active electrode was inserted into a hole in a transparent contact lens mounted on the anaesthetized cornea. The space between the contact lens and the cornea was filled with saline, which connected the electrode tip to the cornea. The tip of the indifferent electrode was placed on the skin near the outer canthus. The pupil was maximally dilated by an instillation of 1% atropine sulfate solution into the conjunctival sac. Potential changes were led to a CR-coupled

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* 米村大藏，河崎一夫

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amplifier with a frequency response flat from 1 to 6,000 c/s, and displayed on a cathode-ray oscilloscope. Upward deflexion indicates positivity of the corneal electrode.

RESULTS

FIG. 1A shows a potential change preceding the a-wave of the human ERG. This potential change is called here tentatively the early potential (EP) for convenience of description. The EP shown in Fig. 1A is biphasic in form, consisting of a small cornea-positive phase followed by a dominant cornea-negative one. The peak latency is 120 μsec for the positive phase, and 800 μsec for the negative one. The positive phase begins immediately at

![Figure 1](image_url)

FIG. 1. The initial segment of the human ERG evoked with an intense photic stimulation (100 joules). Record A was obtained from a normal subject. Note a biphasic response (the EP) preceding the a-wave. The EP was abolished in some pathological states of the eye such as idiopathic total detachment of the retina (B), primary pigmentary degeneration of the retina (C) and phthisis bulbi. Frequency response of the recording system was flat from 1 to 6,000 c/s. This frequency characteristic holds for all records in this paper. In the darkness. The arrow indicates stimulus artefact. Positivity upward.
the end of the stimulus artefact, having a latency of less than 30 μsec. Thus the EP in man is very similar in shape to the ERP in other vertebrates (Brown and Murakami, 1964b; Cone, 1964, 1965; Pak and Cone, 1964; Pak and Ebrey, 1965; Brown, 1965; Brown, Watanabe and Murakami, 1965; Pak, 1965; Arden and Ikeda, 1965, 1966; Brindley and Gardner-Medwin, 1966).

With the intense stimulus light used in the present experiments, the latency of the a-wave was reduced to 1.7 msec, which is the shortest value thus far reported for the a-wave of the human ERG. This value is very close to the minimum latency of the a-wave of some other mammals in which an origin of the a-wave is localized in the visual cells (Brown and Murakami, 1964a; Brown, Watanabe and Murakami, 1965). These facts may support the view that an origin of the a-wave in the ERGs of the vertebrates including the human lies in the visual cells (Auerbach and Burian, 1955; Brown and Wiesel, 1961; Yonemura and Hatta, 1965, 1966; Murakami and Kaneko, 1966).

A question may arise whether the EP comes from the retina or not. If the EP does not originate in the retina, patients with extensive deterioration of the retina might still show the EP. But this was not the case: the EP was not observed in cases of extended impairments of the retina such as idiopathic total detachment of the retina and primary pigmentary degeneration of the retina (Fig. 1B, 1C). The EP can not be involved by reflex blinking or reflex movements of the eyeball in response to photic stimulation for the following reasons. 1) These motor reflexes begin too late after the stimulus to be responsible for the production of the EP. 2) Akinesis of the eyelids and immobilization of the extraocular muscles by a local application of 2% xylocaine solution failed to affect the size and time course of the EP. 3) The EP comparable to the normal control (Fig. 1A) was definitely observed in a subject who had been completely blind because of intracranial lesion of the optic nerve, and who exhibited neither reflex blinking nor reflex movements of the eyeball in response to photic stimulation.

The foregoing evidence indicates that the EP is closely related to the retinal function. The EP had the normal size and time course in long-standing simple atrophy of the optic nerve. Since prolonged optic nerve atrophy is assumed to be associated with degeneration or reduction in number of the retinal ganglionic cells in mammals (James, 1933; Leinfelder, 1940; Eayrs, 1952; Van Buren, 1963; Hogan and Zimmerman, 1964), the EP can not be considered as generated by the retinal ganglionic cells.

Further information on the EP was obtained from a case of obstruction of the central artery of the retina. In the acute stage of this circulatory disturbance, there usually occurs an edema in the inner layers of the retina, which loses its transparency and becomes milky white (Elwyn, 1947). The
loss of the retinal transparency may decrease the effective stimulus intensity at the receptors, as pointed out by Brown, Watanabe and Murakami (1965). In the later stages of this circulatory arrest, the retinal edema gradually subsides. The EP was recorded long after the subsidence of the retinal edema caused by obstruction of the central retinal artery. In this experiment, therefore, we may safely exclude the possibility that the effective stimulus intensity was reduced by the retinal edema. The EP thus obtained showed no significant abnormalities in the size and time course, as compared with the normal control (Fig. 1A). The inner layers as far as the inner nuclear layer are supplied in man by the central artery of the retina, whereas the visual cells have been postulated to be nourished virtually by the choroidal circulation (Polyak, 1957; Michaelson, 1954; Adler, 1965; Hogan and Zimmerman, 1964). Occlusion of the central artery of the retina must abolish responses arising from the inner layers of the retina, without markedly reducing the visual cell activity, as proved by Brown and Murakami (1964a) on the monkey. The preceding argument makes it plausible that the EP depends, at least in part, on the visual cell activity.

This view is supported by an additional evidence described below. The EP was entirely abolished in idiopathic total detachment of the retina (Fig. 1B). In this pathological state of the eye, the function of the visual cells should be considerably reduced, because they are segregated from the pigment epithelium, hence, their immediate source of nourishment (Hogan and Zimmerman, 1964). The EP was also extinguished even in the early stages of degeneratio pigmentosa retinae (Fig. 1C) in which the initial lesions are believed to occur in the visual cells (Hogan and Zimmerman, 1964; Adler, 1965).

The amplitude of the cornea-negative phase of the EP was approximately linearly related to the stimulus intensity for the first 1.1 log units above the threshold. In this range of stimulus intensity, the a- and b-waves showed no significant increase in amplitude. In addition, the EP was far less affected by moderate light adaptation than the ordinary ERG components such as the a- and b-waves. This implies that at appropriate levels of light adaptation the EP can be practically isolated from the ordinary ERG components including the a-wave. The EP seems therefore different in generation mechanism from the a-wave as an index of the receptor activity. Thus we may state that the initial segment of the human ERG is concerned with the two types of the receptor potentials, i.e. the EP and the a-wave.
The EP described here in man closely resembles the ERP in other vertebrates, because (1) it has a similar time course, (2) it can only be evoked with intense photic stimulation, (3) the amplitude of its cornea-negative phase is approximately related to stimulus intensity up to a limit (see Cone, 1964, 1965), and (4) it is probably intimately connected with the visual cell activity. Consequently it seems quite reasonable to assume that the early potential (EP) in man is, so far tested, comparable to the ERP in monkeys (Brown and Murakami, 1964a, b; Brown, Watanabe and Murakami, 1965), cats (Cone, 1964), albino rabbits (Yonemura and Kawasaki, unpublished), albino rats (Cone, 1964, 1965; Pak and Cone, 1964; Pak and Ebrey, 1965; Pak, 1965; Arden and Ikeda, 1965, 1966), pigeons (Yonemura and Kawasaki Fig. 3), tortoises (Kawasaki and Yonemura, Fig. 2, B), frogs (Cone, 1964; Brindley and Gardner-Medwin, 1966), toads (Brown, 1965), goldfish (Cone, 1964). Accordingly we may postulate that the ERP exists in every vertebrate eye.

Fig. 2. Time courses of the EPs of the albino rat (A) and the tortoise (B). Note the new cornea-positive potential occurring between the cornea-negative phase of the EP and the a-wave. In partly dark-adapted animals. The arrow indicates stimulus artefact. Positivity upward. Records A and B were retouched only for clarity of reproduction.
including the human eye. But the possibility can not be excluded here that the EP obtained by a corneal lead in man might be partly contaminated by potentials from the pigment epithelium-choroid complex, as asserted by Brown (1965) on the ERP of the toad.

The ERP thus far reported has been biphasic in form, consisting of a cornea-positive phase followed by a cornea-negative one. Using albino rats, Arden and Ikeda (1966) suggested that the ERP has an additional positive-going component. They did not, however, demonstrate in the ERP any additional deflexion which was actually cornea-positive in polarity. We have detected a new cornea-positive potential in albino rats as well as tortoises which are partly dark-adapted (Fig. 2A, 2B). Although the details on this potential will be published later, some of the essential parts are described below. The summit of this potential appears, as shown in Fig. 2, between the cornea-negative phase of the EP and the leading edge of the a-wave.

Fig. 3. Isolation of the new cornea-positive potential in the pigeon by reducing stimulus intensity. Record A was evoked with the flash of the maximum intensity available in this experiment (100 joules). In record B, the effective stimulus intensity was reduced to one hundredth of the maximum by inserting a neutral density filter in the light path. Note that the peak latency of the new cornea-positive potential coincides with that of the positive-going hump between the cornea-negative phase of the EP and the a-wave (A). In the partly dark-adapted animal, the arrow indicates stimulus artefact. Positivity upward.
This new potential was practically isolated in the pigeon with reducing the stimulus intensity (Fig. 3). A similar potential was also elicited in the cat in the course of asphyxia (Fig. 4). Presumably the reduction in the amplitude of the a-wave results in an apparent increase of the new corneal positive potential which is considerably masked by the a-wave in normal conditions.

The new cornea-positive potential under study is present, as shown above, in the essentially all-rod eye (Dowling, 1963) of the albino rat as well as in the pure cone eye (Granit, 1956) of the tortoise (Fig. 2). Moreover a similar potential is disclosed by asphyxiation in the rod-cone eye (Granit, 1956) of the cat (Fig. 4). On the basis of these facts, the EP of the human eye which has the rods and cones (Duke-Elder, 1961) would be expected to show an additional cornea-positive phase in some conditions. Further experiments on this point are now being undertaken.
SUMMARY

A new rapid potential with a very short latency was reported in the human electroretinogram (ERG). This new potential was tentatively called the early potential (EP). The present experiment gave evidence that the EP in man is essentially identical with the early receptor potential (ERP) in other vertebrates. Intense photic stimulation with a very short rise time was needed to evoke the ERP in man.

1) The EP obtained from normal subjects was seemingly biphasic in form, consisting of a small cornea-positive phase followed by a dominant cornea-negative one. The latency of the cornea-positive phase was less than 30 μsec.

2) The latency of the a-wave elicited with the intense stimulus was as short as 1.7 msec, being the shortest value thus far reported for the a-wave of the human ERG. This may support the view that an origin of the a-wave of the human ERG lies in the visual cells.

3) The amplitude of the cornea-negative phase of the EP in man was approximately linearly related to the stimulus intensity for the first 1.1 log units above the threshold. In this range of stimulus intensity, the a- and b-waves showed no significant increase in amplitude.

4) The EP in man was not so greatly affected by moderate light adaptation as the ordinary ERG components. This implies that at suitable levels of light adaptation the EP can be practically isolated from the ordinary ERG components.

5) The EP comparable in size and time course to the normal control was observed in long-standing simple atrophy of the optic nerve and complete obstruction of the central artery of the retina. The EP was entirely abolished in idiopathic total detachment of the retina as well as even in early stages of the primary pigmentary degeneration of the retina. These findings may indicate that the EP in man is closely related to the activity of the visual cells.

6) A new cornea-positive potential, the summit of which appeared between the cornea-negative phase of the EP and the a-wave, was detected in cats, albino rats, pigeons and tortoises. This finding, coupled with the arguments in this paper, may advance a working hypothesis that the EP shows an additional cornea-positive phase in some conditions.

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