Principles and Practice of Clinical Electrophysiology of Vision

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Retinal Extracellular Potential Responses Not Evoked by Light

Chester Karwoski

POTENTIALS EVOKED BY OPTIC NERVE STIMULATION

The contribution of ganglion cells to the electroretinogram (ERG) has been explored by antidromically activating them via electrical stimulation of the optic nerve. The first to do this were Ogden and Brown,[22, 23] who found in primate retina a field potential that had maximum positive amplitude in the inner plexiform layer and a smaller negativity in the ganglion cell layer. This response, termed the *P-wave*, was also observed in primates by Gouras,[7] but he found a reversal point in the inner plexiform layer and the largest positivity in the inner nuclear layer. A similar response profile was found by Miller et al.[17] in the mudpuppy.

The exact origin of the P-wave is controversial. It was initially thought to arise from activation of inner retinal neurons via the efferent system,[23] but this remains a possibility only in nonmammalian species where retinal efferent innervation has been clearly shown. More recently, arguments have been marshaled for the P-wave arising directly from ganglion cell spikes,[7] from Müller cell spatial buffering of K^+ released by ganglion cells,[17] and from activity in retinal neurons that are postsynaptic to ganglion cells.[22, 28] Other mechanisms may also exist by which activity in ganglion cell axons may induce responses elsewhere in the retina, eg, "blue arcs."[2] It is possible that multiple mechanisms may contribute to the P-wave, and the size of the contribution may depend on the species and experimental methodology. At any rate, it is not certain whether the P-wave arises *directly* from ganglion cell activity.

There is also disagreement whether the P-wave can be recorded transretinally. Studies in primates failed to find such a contribution, but a substantial negativity in the vitreous was seen in the mudpuppy.[17] As with the proximal negative response (PNR) and M-wave, a contribution from the generators of the P-wave to the transretinal ERG has not been ruled out completely, and a possible role in the pattern ERG should be considered.

POTENTIALS EVOKED BY TRANSRETINAL ELECTRICAL CURRENT

Simultaneous electrical stimulation of a single retinal neuron while recording from another is a powerful technique that has been used by several laboratories to elucidate connections between neurons of the proximal retina.[21] In addition, single photoreceptors have been stimulated electrically in order to bypass the visual transduction process.[1] Electric current passed extracellularly across the whole retina (transretinal current) will also generate retinal activity that does not arise via phototransduction. The first to demonstrate this was Motokawa et al.,[20] who passed current across the isolated retina of carp and recorded an electrically evoked ERG (the EERG). The EERG has since been shown to be a general feature of the vertebrate retina.[13, 23]

The EERG has several components, and its analysis will likely prove as complex as the standard light-evoked ERG. In the primate, Ogden and Brown[23] presented evidence that three EERG components arise via current-evoked antidromic activation of

ganglion cells, while two others (early negative wave [EN] and late negative wave [LN]), arise in the inner nuclear layer. The EERG LN and ERG b-wave have nearly identical intraretinal depth profiles, and thus these field potentials may arise through the same underlying processes.[14, 20, 23] However, a comparison of changes in extracellular $[K^+]$ during transretinal current and during the light-evoked b-wave does not clearly support this idea.[11, 12]

Another issue concerns which cells are activated by transretinal current. There is widespread agreement that photoreceptor synaptic terminals are activated[13, 31, 32] and that activity initiated by this process will continue through the rest of the retinal circuitry. Transretinal current will directly activate bipolar-amacrine synapses in the absence of photoreceptor synaptic transmission[31] and even in the absence of photoreceptors.[26] In addition, ganglion cell axons may be activated directly.[23] Direct electrical activation of other retinal cells and synapses should also be considered.

Because the proximal retina can be directly activated by electrical current, the EERG has potential value as a tool for assessing the integrity of proximal retinal neurons during disorders in which photoreceptors have degenerated or are inactive.[25] It may also be useful during disorders in which light cannot reach the photoreceptors (e.g., corneal burns, cataracts, intraocular hemorrhage).

SPREADING DEPRESSION

The phenomenon of spreading depression (SD), first described by Leaõ[15] in cerebral cortex, consists of a slowly propagating and transient depression of neural activity, and it is associated with a host of physiological events, including a large, local field potential. Gouras[8] described SD in amphibian retinas and it has since been observed in many species, including mammals.[16, 27] The field potential associated with retinal SD has maximum amplitude in the proximal retina, possibly at the inner limiting membrane.[19] Within the proximal retina, this potential is negative going, but the transretinally recorded SD potential can be predominately negative or positive, depending on the species.[5] SD is also associated with a large increase in $[K^+]_o$ in the inner plexiform layer, and several lines of evidence suggest that the origin of the SD potential is currents associated with the spatial buffering of this increased $[K^+]_o$ by Müller cells.[18, 19, 24]

The frequency of retinal SD can be increased by events such as injury to a retinal region,[8] mechanical stimulation of the retina,[4] anoxia,[8] application of high concentrations of K ions[10] or low concentrations of Cl ions,[18, 24] application of the excitatory amino acids glutamate or aspartate,[18, 29] light offset,[27] and antidromic stimulation of the optic nerve[18]; seemingly spontaneous SDs have been observed in chick (R.H. Steinberg, personal communication) and lizard eyecups (C.J. Karwoski, unpublished observation). Because of the large number of conditions that facilitate or initiate SDs it seems reasonable that SD will sometimes be associated with disorders of the eye or retina in humans. Although this has not been reported, it is a fruitful topic for future research.[27] Two difficulties are that (1) the retinal SD may be a transient event, and the clinician must be recording an ERG or looking in the eye (for the color change of the retina associated with SD[33]) at the proper time; (2) it is not certain whether a retinal SD could be detected by electroretinography. In vitreal recordings from the eyecup of the lizard Anolis, SDs generate transient positive shifts in potential, following which ERG amplitude is depressed for several minutes (unpublished observation). However, the lizard eye is small, and SD could dominate the recording. An SD in the large eye of humans may depress a relatively small retinal area, and both the SD-induced potential shift and the depression in the ERG that is evoked by diffuse light may be undetectable.

In the brain, increasing evidence points to SD generating many of the symptoms of migraine headaches,[6, 9] and SD occurs in conjunction with stereotaxic surgery.[3] Somjen and Aitkin[30] argue for SD to be considered a transient and propagating type of cortical depression that is initiated at one point, while another type of depression is diffuse and nonpropagating. The latter would possibly include depressions arising during transient cerebral hypoxia (due to asphyxia or to brief failure of cerebral circulation) and during concussions. Because of the number of events possibly related to cortical depressions (both spreading and diffuse) in humans, the clinician should keep alert to the possibility of such depressions in the retina.

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