Principles and Practice of Clinical Electrophysiology of Vision

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16

Oscillatory Potentials

Chester Karwoski
Kazuo Kawasaki

The oscillatory potentials (OPs) of the electroretinogram (ERG) consist of several rapid, low-amplitude potentials, sometimes called wavelets, superimposed on the b-wave. In species from amphibian to primate, the number of OPs averages about seven but can vary from about four to ten. There are two issues regarding their origin: (1) within one ERG, do all of the OPs have the same origin? (2) Which specific cells generate the OPs?

DO ALL THE OPs HAVE THE SAME ORIGIN?

In primates, two studies fail to show differences in the depth profiles of the various OPs[6, 13] (Fig 16–1). A similarity of depth profiles for different responses does not exclude differences in origins, but these studies are consistent in providing no evidence that the various OPs may have different origins. In amphibians, on the other hand, depth profiles are in agreement that the earlier OPs arise near the inner plexiform layer while the later OPs arise more distally, probably within the inner nuclear layer (mudpuppy,[21] frog[23]) (Fig 16–2).

Supporting the idea that the various OPs in the mudpuppy have different origins is the finding that they are differentially sensitive to pharmacological agents. The earlier OPs are depressed by α-aminobutyric acid (GABA) antagonists,[17] the dopamine antagonist haloperidol,[18] β-alanine,[19] and substance P.[20] The later OPs are depressed by the glycine antagonist strychnine[17] and by ethanol.[19]

In conclusion, it is probable that the various OPs in amphibians do not originate in a single cellular process. However, in primates, observations to date are compatible with the possibility of all OPs originating at the same retinal level.

WHICH CELLS GENERATE THE OPs?

Some of the observations described above indicate proximal neurons are important, and this idea is reinforced by other experimental and clinical lines of evidence indicating the OPs arise through mechanisms post-synaptic to the photoreceptors. For example, the OPs are suppressed in cases of occlusion of the central retinal artery, which nourishes the inner and middle retinal layers,[28] and experimental occlusion of the central retinal artery in monkey abolishes the OPs.[3] Also, the OPs are abolished, while the receptor potential remains undiminished, after application of aspartate or glutamate,[25] which is known to block photoreceptor synaptic transmission.

The pigment epithelial (PE) cells and the Muller cells can also be excluded as generators of the OPs. No rhythmic wavelets are observed in light-evoked responses from PE cells,[15] and from Muller cells.[8] Furthermore, OPs are clearly observed in the isolated retina detached from the PE (see Fig 16–2).

Any contribution of ganglion cells to the OPs is probably small. Arguing against a contribution are that OPs remain normal in cases of long-standing optic nerve atrophy[28] and after optic nerve section in rabbit,[22] conditions that should result in ganglion cell degeneration. Furthermore, tetrodotoxin (which

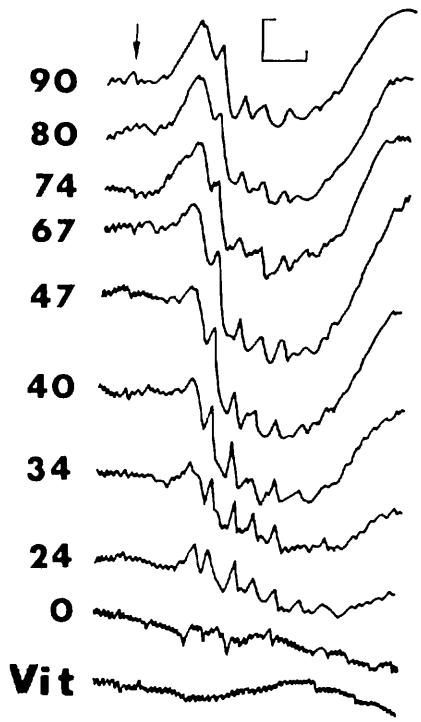

FIG 16–1.
Depth profile of OPs in the retina of a rhesus monkey. Recordings were made as a microelectrode was withdrawn measured distances from Bruch's membrane; numbers to the left indicate the percent retinal depth. The number and time course of the OPs do not significantly change at different retinal depths. The *arrow* indicates the onset of a 50-ms light flash (Calibration. 200 μV, 10 ms).

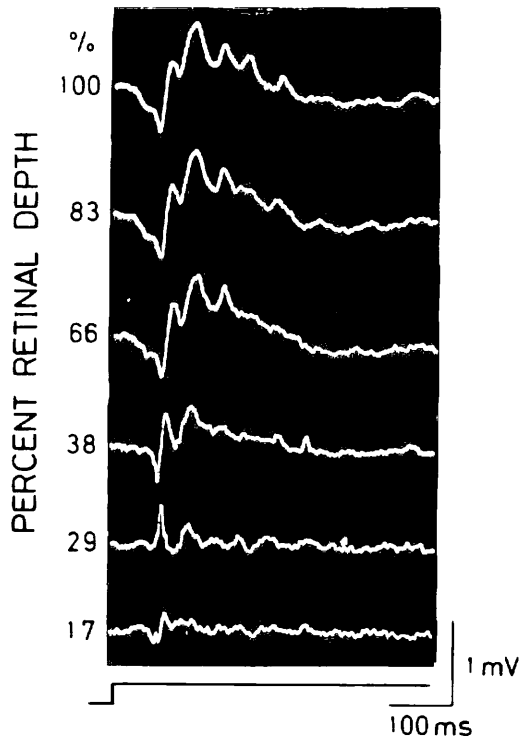

FIG 16–2.
Depth profile of OPs of an isolated frog retina. The intraretinal electrode was introduced from the receptor side, and the reference electrode was placed on the vitreal side. The depth of the electrode tip within the retina is indicated relative to the vitreal surface (0%) and the receptor surface (100%). When the electrode was in the receptor layer (at 100% and 83% depths), five OPs could be identified. As the electrode was advanced proximally, the OPs with longer peak latencies disappeared. (From Yanagida T, Koshimizi M, Kawasaki K, et al: *Doc Ophthalmol* 1988; 67:355–361. Used by permission.)

blocks action potentials) has little effect on OPs in primates.[13, 27] On the other hand, optic nerve section in primates resulted in ganglion cell degeneration and disappearance of the OPs,[13] and antidromic stimulation of the primate optic nerve resulted in a reduction in OP amplitude[13]; however, Ogden also presented reasons why these two observations should be accepted with caution. In summary, a contribution of ganglion cells to the generation of OPs cannot be ruled out but is probably small.

OPs probably originate in the vicinity of the inner plexiform layer. All depth profiles provide evidence for this level of origin,[13, 21, 23] and a current source density analysis in primate also points to the inner plexiform layer.[6] Furthermore, the application of glycine, an inhibitory neurotransmitter localized to the inner plexiform layer, selectively suppresses OPs in vivo (rabbit[9]) and in vitro (rabbit,[24, 26] human[24]), and this suppression is antagonized by strychnine.[24, 26]

Neural interactions are commonly thought to play a major role in the generation of the OPs, and the importance of inhibitory feedback synaptic circuits has been repeatedly proposed. However, it has not been excluded that membrane processes intrinsic to a cell (e.g., rhythmic fluctuations in channel activity) may play a major role in OP generation (H. Sakai and K.I. Naka, personal communication).

COMPARISON TO INTRACELLULAR RESPONSES FROM NEURONS

A comparison of the OPs to intracellular responses of retinal neurons should provide information about which cells could be the OP generators. It

would be best if a survey of intracellular responses were undertaken with simultaneous recordings of ERG oscillations. This has not been done, but there are many hundreds of published papers showing intracellular responses from retinal neurons. The variety of species, stimulus conditions, and response types is immense, but a review of this literature does reveal some important trends.

Oscillations are not observed on the light-evoked responses of rods, cones, or horizontal cells. Dark oscillations have been described in rods and horizontal cells,[12a] but these are abolished by light onset. A slight "ringing" is sometimes observed at the peak of the on-responses of these cells, but this ringing cannot account for OPs, because it has only two to three cycles at most, its duration is short, and its amplitude is small.

Of the approximately 100 articles showing bipolar cell recordings, oscillatory-like responses are shown in only one—that of Marchiafava and Torre.[10] They show one to two oscillations, at about 20 Hz, in both a depolarizing and a hyperpolarizing bipolar cell in the turtle.

A sizable number of articles on turtles and fish show oscillations on amacrine cell responses. Depolarizing sustained-on amacrine cells show oscillations most reliably,[4, 11, 16] and these have been studied most intensively by Naka's laboratory[14] (Fig 16–3). Oscillations in these cells could number more than ten, and they arise at a frequency of 30 to 50 Hz, which is similar to the frequency of OPs in the carp ERG (40 Hz[1]). Depolarizing on/off amacrine cells show oscillations at the same frequency, but their appearance is less reliable.[4, 10, 11, 14, 16] Finally, hyperpolarizing amacrine cells never show oscillations at light onset,[4, 14] but they may contribute to OPs at light offset.[14]

Intracellular responses of interplexiform cells have been reported in only two studies. Hashimoto et al.[5] show a response from one depolarizing cell with three to four oscillations occurring at about 40 Hz. In the mudpuppy, R.F. Miller (personal communication) finds interplexiform cell responses to be like horizontal cell responses, but slower.

It was argued above that any ganglion cell contribution to OPs was likely to be small. Intracellular recordings from these cells support this idea in that there are very few reports of oscillations on the light-evoked intracellular potentials. In the mudpuppy, Belgum et al.[2] show an on/off ganglion cell response with three to four oscillations occurring at 1 to 2 Hz. However, since the frequency of the ERG

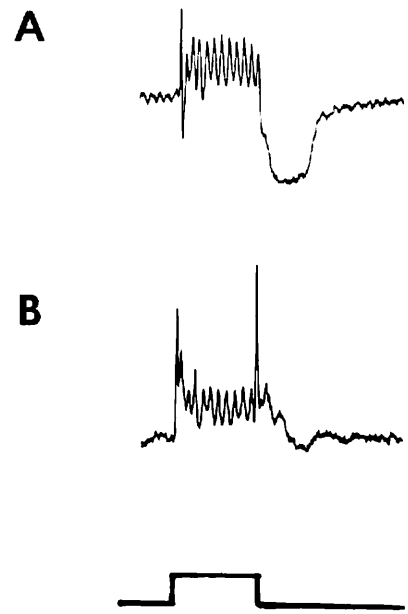

FIG 16–3.
Light-evoked intracellular responses recorded from amacrine cells in a catfish retina. **A**, sustained-on, or type N, neuron. Oscillations are regularly present during light onset. **B**, transient-on/off, or type C, neuron. Only some type C neurons (including this one) exhibited oscillations (stimulus duration, 0.5 seconds). (From Sakai H, Naka K-I: *Prog Ret Res* 1988; 7:149–208. Used by permission.)

OPs in the mudpuppy is much higher (15 to 30 Hz[21]), the oscillations in ganglion cells reported by Belgum et al.[2] cannot contribute to the ERG OPs. In catfish, Sakai and Naka[14] imply that a few ganglion cells show oscillations. Karwoski and Proenza[7] showed that oscillations at 10 to 15 Hz in the light-evoked field potential of the proximal retina correlated with on/off ganglion cell spikes, but not with on- or off-cell spikes. Thus, oscillatory events in inner retinal neurons may play a role in generating spike discharges in some ganglion cells, but the ERG OPs are unlikely to arise from ganglion cells.

Overall, depolarizing amacrine cells, particularly those producing sustained responses at light onset, appear to be the prime candidates for generators of the ERG OPs. On/off amacrine cells possibly make a smaller contribution. Any contribution from interplexiform cells cannot yet be assessed: the rarity of recordings from these neurons might mean that they are sparsely distributed as compared with amacrine cells and thus make a smaller contribution to the ERG; however, since their anatomical connectivity and orientation are more characteristic of a radial dipole than in the case of amacrine cells, the contribu-

tion of interplexiform cells to the ERG may be relatively large.

CONCLUSIONS

Experiments in some cold-blooded vertebrates support the idea that the ERG OPs derive from depolarizing amacrine cells and possibly also from depolarizing interplexiform cells. In addition, the findings in mammals (including humans and nonhuman primates) do not conflict with this idea. Thus, it is possible that OPs may be used as a rather selective probe of certain neural circuits in the proximal retina.

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