Principles and Practice of Clinical Electrophysiology of Vision

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Mosby-Year Book, Inc.
11830 Westline Industrial Drive
St. Louis, MO 63146

1 2 3 4 5 6 7 8 9 0 CL CL MV 95 94 93 92 91

Library of Congress Cataloging-in-Publication Data
Principles and practice of visual electrophysiology / [edited by]
John R. Heckenlively, Geoffrey B. Arden.
p. cm.
Includes bibliographical references.
Includes index.
ISBN 0-8151-4290-0
1. Electroretinography. 2. Electrooculography. 3. Visual evoked response. I. Heckenlively, John R. II. Arden, Geoffrey B. (Geoffrey Bernard)
[DNLM: 1. Electrooculography. 2. Electrophysiology. 3. Electroretinography. 4. Evoked Potentials, Visual. 5. Vision Disorders—physiopathology. WW 270 P957]
RE79.E4P75 1991 91-13378
617.7 1547—dc20 CIP
DNLM/DLC
for Library of Congress

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Intensity Relations and Their Significance

Anne B. Fulton

The hyperbolic function $V/V_{max} = I^n/(I^n + \sigma^n)$ (Equation 1) reasonably well describes[1–4] the relationship of the rod a- and b-wave potentials, V, to stimulus intensity, I. The value of I that produces a half-maximum response is σ. The log-log plot of this function (Fig 31–1) shows that response voltages increase linearly as low-intensity lights are incremented and then, as I is increased further, approach a maximum. The exponent n indicates the slope of the linear portion of the curve. If $n = 1$, as it does for b-waves from normal eyes[2, 12, 19, 26, 41] and most but not all abnormal eyes,[2, 5–7, 11, 12, 16, 23, 26, 29] the linear range covers about 1.8 decadic log units of stimulus intensity.[36]

In the first reports to recognize explicitly that the response voltage of distal retinal cells was related to stimulus light intensity according to Equation 1, Naka and Rushton[31, 32] noted that this mathematical function also represents a logistic growth curve[37] such as describes the growth of the U.S. population between 1790 and 1940. Perhaps more relevant to changes in potential across the membranes of retinal cells are models of enzyme[27] or adsorption[25] kinetics that are cast as the hyperbolic function summarized by Equation 1. Physical events fulfilling the prediction of these models[25, 27] are enzyme velocities that increase linearly as substrate is added until, with saturation of enzyme sites, velocities approach a maximum,[27] or adsorption of particles on a surface proceeds linearly until sites become occupied, and no matter how many more particles are made available, the rate of adsorption reaches a never-to-be-exceeded rate.[25]

The observed relation of the mass response of rods[34] and of individual rods,[20] cones,[3, 4] and second-order retinal neurons[31, 32, 42, 43] to stimulus intensity also conforms to Equation 1. Photoreceptors generate the a-wave.[35] The glial cells of Müller generate the b-wave, which indirectly indexes the activity of second-order neurons.[1, 10, 28] Thus, it is not surprising that the a- and b-waves of the electroretinogram (ERG)[18, 19] show similar stimulus/response (S/R) functions to those of the neural cells underlying the generation of these mass potentials.[40]

Prior to microelectrode studies of cellular S/R functions,[3, 4, 10, 20, 28, 31, 32, 34, 35, 42, 43] the b-wave S/R functions reported for normal and abnormal eyes[8, 9, 38, 39] lacked the physiologically based interpretations now possible; retrospective interpretation of some of these studies is difficult because test conditions (mainly stimuli) are incompletely specified. Even in light of the cellular data and similarities between cellular[1, 3, 4, 10, 20, 28, 31, 32, 34, 35, 42, 43] and ERG[1, 2, 5–7, 10–14, 16, 18, 19, 23, 26, 28, 29, 41] S/R functions, there are differences that bear on interpretation of a- and b-wave S/R functions. In brief, ERG S/R functions are less steep (n of Equation 1 is smaller), less sensitive (log σ), and lower in voltage (V_{max}) than the S/R functions of the neural cells presumed to produce the a- and b-waves. Explicit and precise explanations for these differences remain incomplete, although current work on relevant models is promising.[22]

The effects of development[12, 14, 15, 21] and aging,[39] photoreceptor degenerations,[2, 5–7, 11, 12, 16, 26, 29] and retinal vascular diseases[23, 38] on S/R curves have been studied. Sensitivity (σ), n, and amplitude (V_{max}) can be examined separately. Such an approach offers an opportunity to consider cellular mechanisms. At present there are strong suggestions that disease-caused attenuation of amplitudes (V_{max}), sensitivity (σ), or perturbations of n of ERG S/R functions often

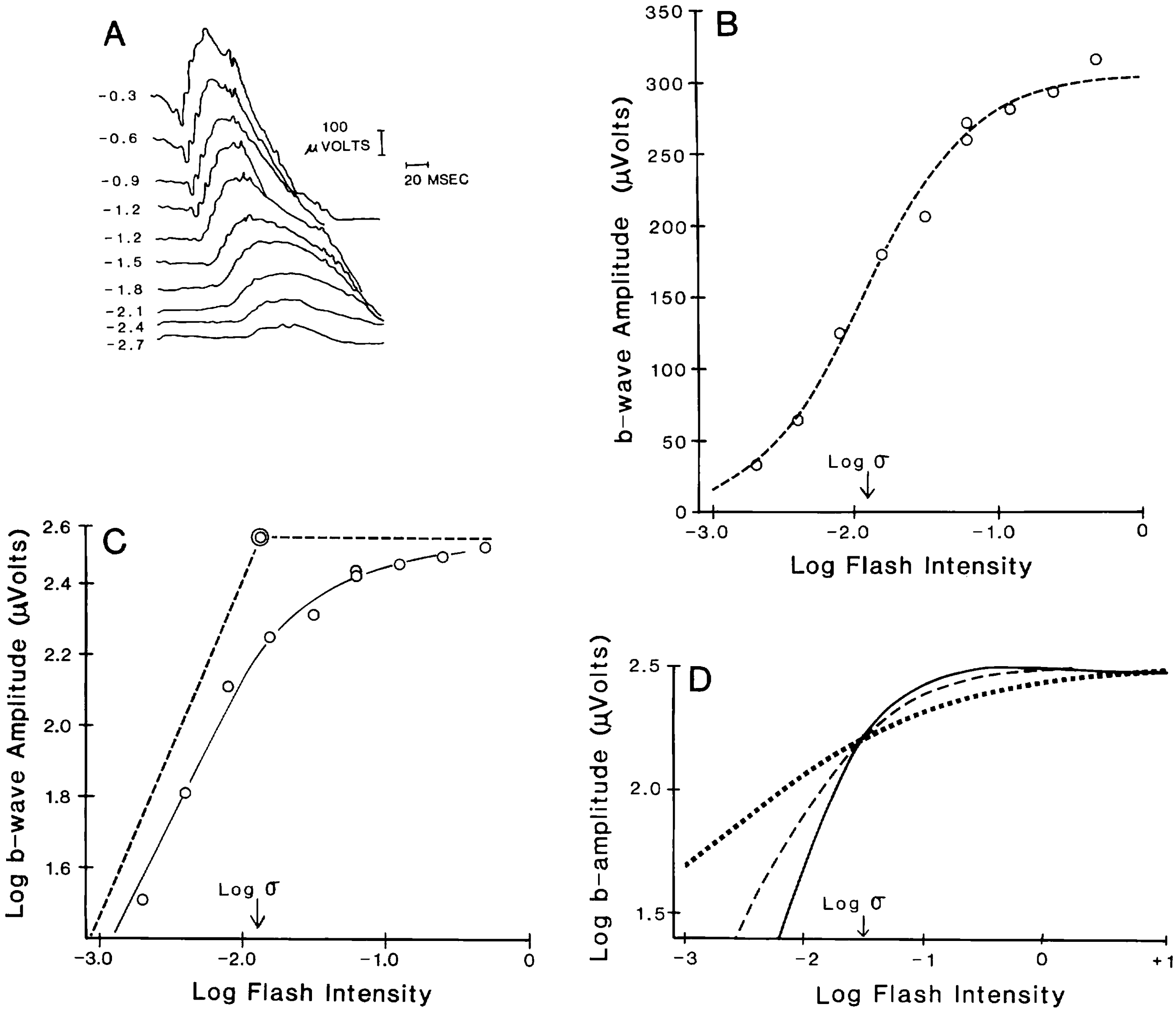

FIG 31–1.

The stimulus/response (S/R) function. **A**, the b-wave responses of a normal subject increase with increasing intensity of strobe flash. The neutral-density filters attenuating the stimulus are indicated to the *left* of each trace; *0* corresponds to a retinal illumination of +1 log scotopic Td second. **B**, the trough to peak amplitudes of the b-wave responses shown in **A** are plotted as a function of log stimulus intensity. The arrow indicates log σ, the flash intensity that elicits a half-maximum amplitude b-wave. The smooth curve represents Equation 1 (see the text) with $n = 1$. **C**, the data of **A** and **B** are shown on log-log coordinates. The asymptotes to the oblique and horizontal limbs of the curve intersect at a point having coordinates the log σ, log V_{max} and, thus, provide a compact representation of these two S/R parameters. **D**, the plots of Equation 1 show that the larger the *n*, the steeper the function. The *dashed curve* is for $n = 1$, *heavy broken curve* for $n = 0.5$, and the *solid curve* for $n = 1.5$.

indicate underlying cellular pathology rather than merely a dropout of cells, loss of rhodopsin, or simple response compression.[2, 13]

To record S/R curves such as shown in Figure 31–1, stimulus intensities need be sufficiently low to establish the linear portion of the relation and sufficiently high that V_{max} can be defined. In practice, stimulus increments of 0.3 to 0.5 log units usually produce data sets to which the three parameters of Equation 1 can be fit when using procedures that minimize the root mean square deviation of the observed responses from Equation 1. Larger step sizes and fewer experimental points reduce the precision with which the parameters of Equation 1 can be determined. Some have found two-parameter *(V, I)* fits satisfactory if conditions are such that n is close to unity.

In retinal degenerative disorders or in early infancy, the range of response amplitudes between the noise level and saturation is attenuated, and signal averaging becomes a necessity to improve the signal-to-noise ratio. Signal averaging is most effectively used when retinal adaptation level is steady. Then testing can be conducted so that repeated stimulations do not attenuate the response. The on-line observation of the trough-to-peak amplitudes of successive b-waves is often used to make this determination. At high stimulus intensities 60-second or longer intervals may be necessary.

Providing intersubject variability is given appropriate consideration, short-cut procedures,[17] including those analogous to linearization procedures (such as Eadie or Lineweaver-Burk methods[30]) used to treat enzyme kinetics, may be suggested to determine log σ and V_{max} if the data delineate the first-order portion of the S/R function.

Responses to test lights that uniformly stimulate as much of the retina as possible are more readily interpreted than those elicited by smaller, nonuniform fields. An integrating sphere or flash lamp and diffuser are used at close range. While recognizing that the integrating sphere does not provide uniform intensity of stimulation to the entire retina[24] and that nearly identical S/R functions are obtained from normal subjects with less than "full-field" and with "full-field" stimulation, valid comparisons of responses from normal retinas and those having disorders affecting the area of responding retina require full-field, uniform stimulation.

Procedural and technical explanations are usually offered for S/R functions that fail to show saturation at higher intensities. These include the failure to limit responses to one class of photoreceptors and, especially at higher stimulus intensities, repetition rates that suppressed amplitudes of subsequent responses. If care is taken to subtract cone responses,[5–7] resulting scotopic S/R functions are in good agreement with previously reported[2, 19] human scotopic b-wave S/R functions that saturate. It has been suggested that higher-than-predicted amplitudes of scotopic b-waves result from algebraic summation of the ERG components.[33]

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