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The luminance–response function of the human photopic electroretinogram: A mathematical model

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Abstract

The luminance–response function of the brief flash full-field photopic electroretinogram (ERG) rises to a peak before falling to a submaximal plateau – the 'photopic hill'. The combination of on- and off-responses inherent in the brief flash photopic ERG suggests that this luminance–response function could be modelled by the sum of a Gaussian function and a logistic growth function. Photopic ERGs to a luminance series of brief flashes against three different background luminances recorded from seven healthy adults showed the characteristic 'photopic hill' function for b-wave amplitudes which were satisfactorily fitted with the sum of a Gaussian curve and a logistic growth curve. As background luminance increased, both components shifted to the right on the luminance axis. The Gaussian component increased in amplitude while the logistic growth function component decreased in amplitude. The luminance–response function of a complete congenital stationary night blindness patient had almost no logistic growth component.

Keywords: Photopic electroretinogram; Mathematical model; Luminance–response function

1. Introduction

The luminance–response function of the full-field photopic (cone-dominated) ERG 'b-wave' to brief flashes demonstrates a peak followed by a non-zero plateau, which has been termed the 'photopic hill' (Wali & Leguire, 1992). The brief flash 'b-wave' is a concatenation of some or all components of the b-wave (on-response)[1] and d-wave (off-response) to a prolonged flash (Sieving, 1993). The unique shape of the photopic hill is a result of two factors: at higher flash luminances, the on-response amplitude reduces and the positive peak of the off-response becomes delayed (Ueno, Kondo, Niwa, Terasaki, & Miyake, 2004). Thus far, no model has been constructed to describe the photopic luminance–response function, although quantification has been performed using typical values (Rufiange et al., 2003).

On-responses (b-waves) demonstrate a logistic growth luminance–response function – the sigmoidal function described by the Naka-Rushton equation in order to fit rod ERG amplitude data with luminance–response curves. Meanwhile, off-responses (d-waves) show a luminance–response function which rises then falls to zero amplitude, i.e. a Gaussian-type curve (Kondo et al., 2000; Kupenova, Vitanova, Popova, & Mitova, 1997). Other off-responses (i-waves and late oscillatory potentials (OPs)) also show Gaussian-like luminance–response functions (Kojima & Zrenner, 1978; Nagata, 1963; Rousseau, McKerral, & Lachapelle, 1996; Rufiange, Rousseau, Dembinska, & Lachapelle, 2002). For these reasons, a mathematical model based on the sum of a logistic growth function and a Gaussian function suggested itself as a means of

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[1] For clarity, where the terms 'on' and 'off' refer to the stimulus (e.g. onset and offset of light), lower case is used. If the terms refer to retinal pathways (e.g. ON and OFF pathway), upper case is used.

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quantifying the luminance–response function of the photopic ERG b-wave to a brief flash. Such a model could allow objective analysis of the function, and enhance investigation of the effects of development and disease on the photopic retinal pathways.

The aims of this study were to construct a mathematical model of the photopic luminance–response function, to test the model with normal human ERG data obtained against various background luminances and to compare normals with a patient with complete congenital stationary night blindness (CSNB1).

2. Methods

A prospective study was designed to examine the photopic hill in human subjects. Seven adult Caucasian humans (age range 29–58; median 35 years) with normal vision and a subject aged 15 years with CSNB1 had a pupil dilated with cyclopentolate 0.5% and the non-test eye patched with a light-occluding patch. All tests were performed in an artificially-lit test room with subjects pre-adapted for at least 15 min prior to testing; the room remained lit throughout the procedure. Dilated pupil sizes were measured before and after the procedure using a half-millimeter scale: diameters ranged from 6.5 to 8.5 mm (mean 7.5 mm) and remained unchanged. The tenets of the declaration of Helsinki were followed and informed consent was obtained from all subjects after explanation of the nature and possible consequences of the study. The study was approved by the local ethics committee.

2.1. ERG procedure

For the normal subjects, white flashes were generated by a xenon discharge lamp (Novatron, Dallas, Texas) in a Ganzfeld bowl and modified by a combination of altered power levels and glass neutral density filters (Coherent Inc., Watford, UK). Sixteen flash luminance levels were presented ranging from 0.05 to 1431 phot cd s m^{-2} in approximately 0.25 log unit steps. An inter-stimulus interval of three seconds was used to ensure full lamp recharge and therefore reproducible flash energy. An interval of approximately 30 s was allowed between flash luminances. Flash order was randomised to avoid adaptation effects, although flash order (increasing or decreasing luminance) has been shown not to affect the photopic hill (Wali & Leguire, 1992). Three luminance–response series were recorded from each subject with Ganzfeld background luminance levels of 67, 26 and 1.6 phot cd m^{-2}, in randomised order, allowing a period of adaptation to each background. Time integrated flash luminance and background luminance were calibrated using a radiometer fitted with a filter which mimicked the CIE photopic sensitivity curve of the human eye in integrating or steady-state modes respectively (IL1700, International Light Inc., Newburyport, MA).

ERGs were recorded using a bipolar Burian-Allen contact lens electrode (Hansen Labs, Iowa) with a silver silver-chloride 'ground' electrode placed on the subject's mastoid. Lubricating drops (Allergan, High Wycombe, UK) and local anaesthesia (proxymetacaine 0.5%) were instilled to aid comfort and improve electrical contact, and repeated throughout the test procedure as necessary. Signals were amplified and filtered with a bandpass of 0.3–300 Hz before being passed to a custom-built acquisition and analysis system, which performed analogue to digital conversion at 2000 Hz and on-line alternating averaging. ERGs contaminated with eye movement or blink artefacts were manually rejected prior to averaging. A minimum of two reproducible ERGs were acquired at each flash luminance to ensure stable amplitudes and averaging was used in low-signal conditions.

Testing for the CSNB subject followed the above protocol except that only one luminance–response series was recorded to the 26 cd m^{-2} luminance background. A DTL fibre electrode referenced to the ipsilateral outer canthus and the Espion® electrophysiology system (Diagnosys LCC, Boston, MA) and ColorDome® Ganzfeld stimulator were used. Flashes from 0.02 to 20 phot cd s m^{-2} were generated by LEDs and those from 50 to 1000 phot cd s m^{-2} were generated by a xenon discharge lamp. Data is presented descriptively because of the amplitude discrepancy between Burian-Allen and DTL electrodes. In our lab, for photopic ERGs, the Burian-Allen : DTL amplitude ratio is 1:1.7, in keeping with findings elsewhere (Esakowitz, Kriss, & Shawkat, 1993). To test comparability of the two systems, one normal adult volunteer was tested with a bipolar Burian-Allen electrode using both the Espion®/ColorDome® system and the custom-built system: the photopic luminance–response functions obtained showed excellent agreement.

Curves were fitted to b-wave amplitude data using non-linear regression analysis (SigmaPlot version 8.0), with goodness-of-fit quantified with R^2 values. A new equation was constructed to model the photopic hill which is the sum of an un-normalised Gaussian curve and a logistic growth curve, given by

$$V_b = G_b\left[\left(\frac{I}{\mu}\right)^{\frac{\ln(\mu/I)}{B^2}}\right] + \frac{V_{b\max} I}{I+\sigma_b}, \quad (1)$$

where V_b is b-wave amplitude measured from the trough of the a-wave. The first term of the equation is a Gaussian curve where G_b is the maximal Gaussian amplitude (μV), I is flash luminance (phot cd s m^{-2}), μ is peak flash luminance at which the maximal amplitude G_b occurs (phot cd s m^{-2}) and $B = \sqrt{2}\,\sigma_G/\log e$, a measure of the width of the Gaussian curve where σ_G is its standard deviation. The second term of the equation is a logistic growth curve (Naka-Rushton function) where $V_{b\max}$ is maximal, saturated amplitude (μV) and σ_b is the semi-saturation flash luminance which evokes a half-maximal response (phot cd s m^{-2}) (Fig. 1). To minimise the number of free parameters and in keeping with studies of the on-response b-wave, the slope parameter was taken to be unity (Popova, Kupenova, Vitanova, & Mitova, 1995; Sieving, 1993). Parameters G_b, μ, B, $V_{b\max}$ and σ_b were allowed to vary to optimise the fit. Parameters of each equation were compared for individuals across the three background luminance levels using repeat measures ANOVA.

3. Results

ERGs to at least 14 (range 14–16) different flash luminances were recorded from each subject. A typical normal adult and the CSNB1 patient series are shown in Fig. 2.

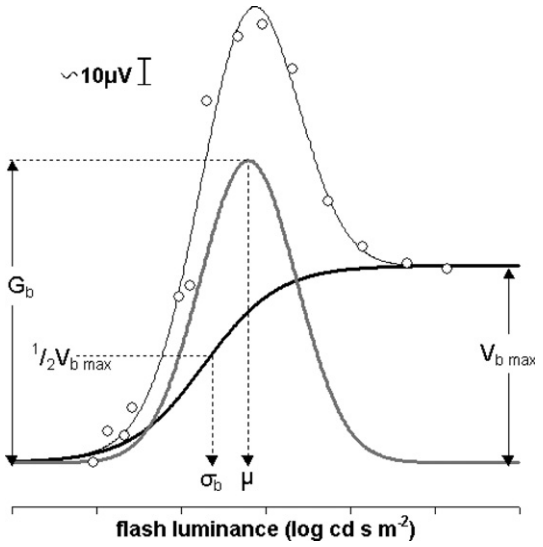

Fig. 1. Graphical representation of Eq. 1, the photopic luminance–response model, for a representative data set. Thin line: Eq. 1 fitted to ERG b-wave amplitude data. Thick grey line: Gaussian function. Thick black line: logistic growth function. The Gaussian and logistic growth functions sum to create the photopic luminance–response model.

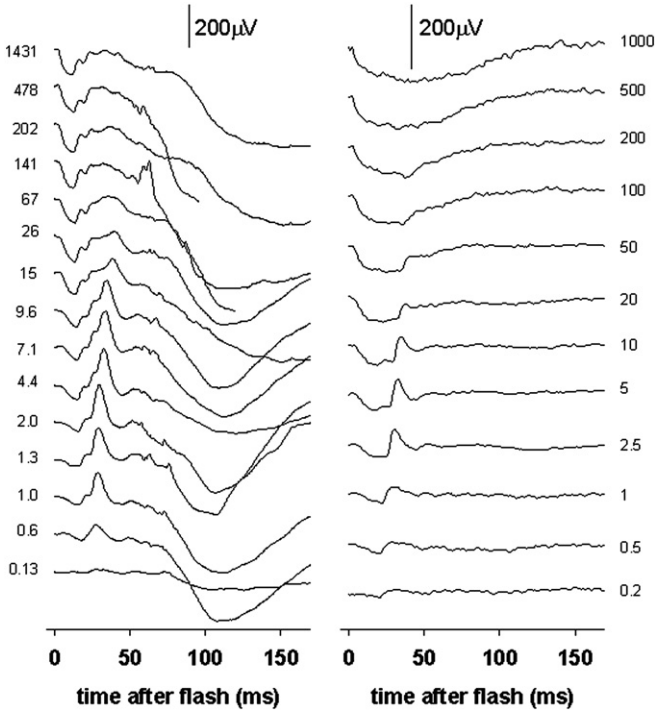

Fig. 2. Typical ERG series obtained from one normal subject (left; Burian-Allen electrode) and the CSNB1 patient (right; DTL electrode). Flash luminance (phot cd s m^{-2}) is shown beside each ERG. Background luminance: 26 cd m^{-2}. The 200 μV scale bars are shown in the ratio 1:1.7, corresponding to Burian-Allen:DTL amplitude ratios.

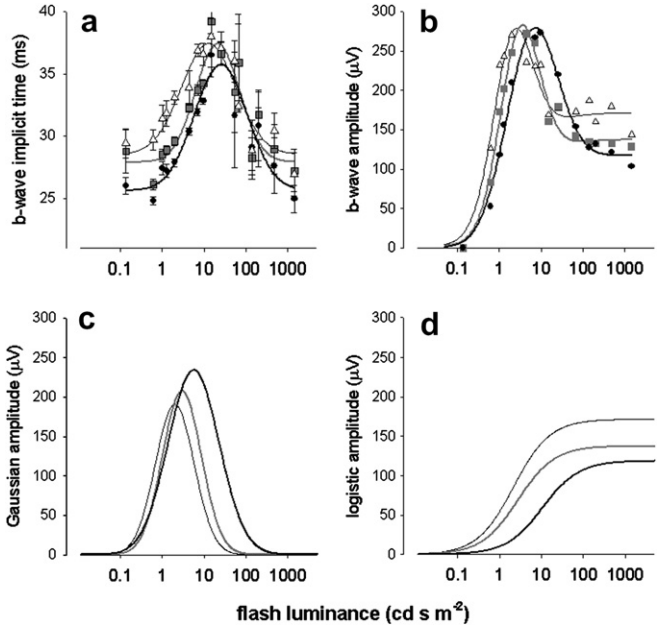

Fig. 3. (a) b-Wave IT versus flash luminance (mean and standard errors) of data from all seven normal subjects and (b) b-wave amplitude luminance–response functions for one typical subject. Lines represent best non-linear regression fits of Eq. (1) to the data. (c) Gaussian function components and (d) logistic growth function components for regression curves in (b). Throughout: circles and thick black line, 67 phot cd s m^{-2} background; squares and thick grey line, 26 phot cd s m^{-2} background; triangles and thin black line, 1.6 phot cd s m^{-2} background.

Implicit time (IT) of the b-wave peak lengthened then shortened with increasing flash luminance. Paired comparisons across all flash stimuli showed small but significant decreases in IT with brighter backgrounds. Increased variability in b-wave IT at higher flash luminances reflects the increased uncertainty created by the intrusion of oscillatory potentials (Fig. 3a).

b-wave amplitude data showed the characteristic photopic hill for all subjects with all background luminances and the data were well fitted by the photopic hill equation (Eq. (1)) (mean $R^2 = 0.97$, range 0.94–1.00). Example hills for a typical subject illustrate the shift to higher luminance with brighter backgrounds, but stable peak amplitudes (Fig. 3b). Corresponding Gaussian and logistic growth components are shown in Fig. 3c and d. Gaussian amplitude (G_b) and peak flash luminance (log μ) both increased with brighter backgrounds ($F = 11.078$, $df = 2$, $P = .002$ and $F = 37.854$, $df = 2$, $P = .000$, respectively). The width of the Gaussian component (log B) did not change with background luminance ($F = 1.478$, $df = 2$, $P = .267$) and was relatively invariant across individuals (mean 0.22 log phot cd s m^{-2}, standard deviation 0.04). The logistic growth component was affected by background luminance with peak amplitude, $V_{b\,max}$, reducing ($F = 5.315$, $df = 2$, $P = .022$) and semi-saturation luminance, log σ_b, increasing ($F = 2.830$, $df = 2$, $P = .098$) with brighter backgrounds. Individual and group parameter data are shown in Fig. 4.

The peak amplitude of the Gaussian component (G_b) increases by 32% from the dimmest to brightest back-

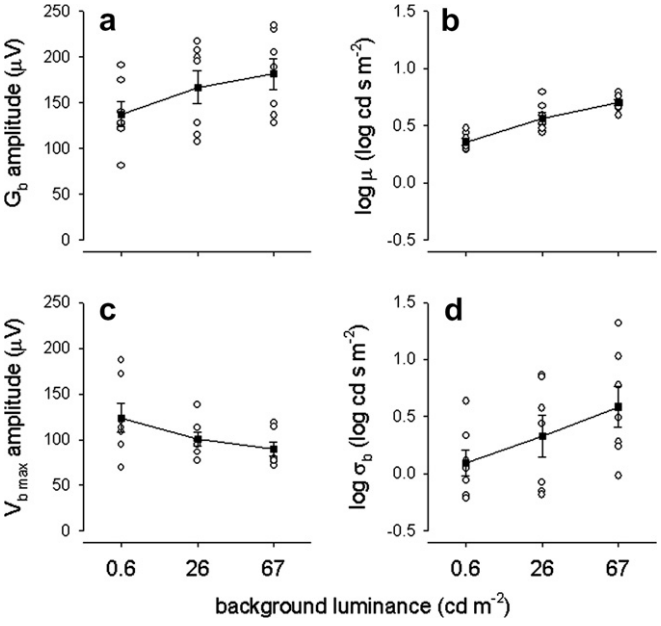

Fig. 4. Effect of background luminance on parameters of Eq. (1). (a) peak Gaussian amplitude (G_b) (b) luminance at Gaussian peak (log μ) (c) maximal, saturated amplitude of the logistic component ($V_{b\,max}$) (d) semi-saturation luminance evoking a half-maximal response of the logistic component (log σ_b). Circles, individual data points; squares, mean data values (error bars, standard errors).

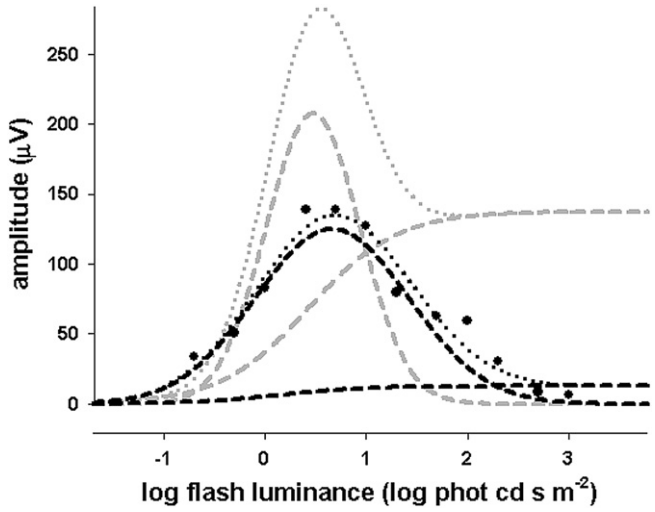

Fig. 5. Luminance–response function recorded from a CSNB1 subject using a DTL electrode (circles and dotted black lines). Dashed black line: Gaussian and logistic growth components for CSNB1 subject. Data scaled by 1.7 (Burian-Allen:DTL amplitude ratio) to allow approximate comparison against normal data (acquired using Burian-Allen electrode) and shown with grey dotted and dashed lines representing median luminance–response curve, Gaussian component and logistic growth component.

ground studied, while there is a smaller relative decrease of 20% in maximal amplitude of the logistic growth function component ($V_{b\,max}$). Both components are shifted to the right by increasing background luminance, with the Gaussian ($\log \mu$) shifting by a mean of 0.34 log units and the logistic growth curve ($\log \sigma_b$) shifting by a mean of 0.49 log units.

3.1. Complete CSNB

Photopic ERGs recorded from the CSNB1 subject show the expected prolonged a-wave with delayed and diminished b-waves (Fig. 2, right). The luminance–response function is fitted by a Gaussian function with no significant logistic growth component (Fig. 5). The b-wave amplitude peak was at 5 cd s m^{-2}. The b-wave ITs ranged from 28 to 50 ms, similar or greater than normal adult ITs.

4. Discussion

Recording a photopic hill is less time consuming and technically less demanding than recording rapid-on and rapid-off (prolonged flash) ERGs and could be a useful way to probe disease, especially in paediatrics or in less co-operative patients. The equation constructed here fits well to experimental data.

The photopic hill and subsequent plateau was first noted when higher luminances were used (maximum 3.34 log phot cd s m^{-2}) (Wali & Leguire, 1992). The current study also uses a wide range of luminances (maximum 3.16 log phot cd s m^{-2}) and thus also defines the plateau. We therefore recommend using flash stimuli up to at least 3 log phot cd s m^{-2} to fully define the luminance–response function in human adults.

4.1. Effect of background adaptation

Background illumination causes changes in sensitivity of cone photoreceptors, via response compression, pigment bleaching or cellular adaptation (Valeton & van Norren, 1983). The photopic luminance–response function is shifted to the right for brighter backgrounds but its peak amplitude remains unaffected, as has been reported elsewhere (Rufiange et al., 2003, 2002). Using the present model, we have demonstrated that the Gaussian component increases in size by 32% from the dimmest to brightest background studied, while there is a smaller relative decrease of 20% in amplitude of the logistic component. Increasing the background luminance shifts the Gaussian component by 0.34 log units to the right compared with 0.49 log units for the logistic growth curve. These relative shifts are also seen in the frog retina, where increasing background luminance causes a larger shift to the right for on-responses (b-waves) than for off-responses (d-waves) (Popova et al., 1995), suggesting that the logistic growth component may be associated with on-responses while the Gaussian component may be associated with off-responses. The net effect is to shift the photopic luminance–response function of the brief flash b-wave to the right without changing its maximal amplitude as background luminance increases: however, this constancy in amplitude conceals possibly opposing on- and off-response changes to background luminance.

4.2. ON and OFF pathway involvement

The b-wave of the brief flash photopic ERG reflects interaction (although not addition) of the rapid on-response (b-wave) and the rapid off-response (d-wave) evoked with a prolonged stimulus (Kondo et al., 2000; Seiple & Holopigian, 1994). The rapid on-response and the rapid off-response are both a result of positive contributions from depolarising bipolar cells (DBC) in the ON pathway *and* negative contributions from hyperpolarising bipolar cells (HBC) and horizontal cells in the OFF pathway – the 'push-pull' model of the photopic b-wave (Sieving, Murayama, & Naarendorp, 1994). Differences in timing and amplitude of contributions from the ON and OFF pathways create the b- and d-waves.

In CSNB1, abnormal on-responses (reduced and delayed b-waves) but normal off-responses (d-waves) are reported (Khan, Kondo, Hiriyanna, Bush, & Sieving, 2005; Quigley et al., 1996). The luminance–response function of the brief flash b-wave for our CSNB1 patient shows almost no logistic component but a normal Gaussian component, further suggesting an association between the logistic growth component and on-responses and between the Gaussian component and off-responses. By visual inspection, this agrees with previous findings for the

photopic luminance–response function in CSNB1 (Rufiange et al., 2003). Blockade of the ON pathway in primates mimics complete CSNB electroretinographically, suggesting that CSNB1 is a disorder of the ON pathway DBCs and spares the OFF pathway (Khan et al., 2005). Further investigation of the photopic luminance–response function in X-linked retinoschisis and incomplete CSNB, which show evidence of disruption to both DBC and HBC function, may add to our understanding of any relationship between on- and off-responses, ON and OFF pathways and the mathematical model presented here. Such quantification may allow exploration of conditions presenting with abnormalities of the ON and OFF pathways, which have hitherto been studied with prolonged flash stimuli (Sieving, 1993).

References

Esakowitz, L., Kriss, A., & Shawkat, F. (1993). A comparison of flash electroretinograms recorded from Burian Allen, JET, C-glide, gold foil, DTL and skin electrodes. *Eye, 7*, 169–171.

Khan, N. W., Kondo, M., Hiriyanna, J. A. J., Bush, R. A., & Sieving, P. A. (2005). Primate retinal signaling pathways: Suppressing ON-pathway activity in monkey with glutamate analogues mimics human CSNB1-NYX genetic night blindness. *Journal of Neurophysiology, 93*, 481–492.

Kojima, M., & Zrenner, E. (1978). Off-components in response to brief light flashes in the oscillatory potential of the human electroretinogram. *Albrecht von Graefs Archiv für Klinische und Experimental Ophthalmologie, 206*, 107–120.

Kondo, M., Piao, C.-H., Tanikawa, A., Horiguchi, M., Terasaki, H., & Miyake, Y. (2000). Amplitude decrease of photopic ERG b-wave at higher stimulus intensities in humans. *Japanese Journal of Ophthalmology, 44*, 20–28.

Kupenova, P., Vitanova, L., Popova, E., & Mitova, L. (1997). Influence of picrotoxin and strychnine on the spectral sensitivity of the turtle ERG b- and d-wave: I. Dark adaptation. *Acta Physiologica Scandinavica, 159*, 217–225.

Nagata, M. (1963). Studies on the photopic ERG of the human retina. *Japanese Journal of Ophthalmology, 7*, 96–124.

Popova, E., Kupenova, P., Vitanova, L., & Mitova, L. (1995). ERG OFF response in frog retina: Light adaptation and effect of 2-amino-4-phosphonobutyrate. *Acta Physiologica Scandinavica, 154*, 377–386.

Quigley, M., Roy, M.-S., Barsoum-Homsy, M., Chevrette, L., Jacob, J.-L., & Milot, J. (1996). On- and off-responses in the photopic electroretinogram in complete-type congenital stationary night blindness. *Documenta Ophthalmologica, 92*, 159–165.

Rousseau, S., McKerral, M., & Lachapelle, P. (1996). The i-wave: Bridging flash and pattern electroretinography. *Functional Neuroscience, EEG Supplement, 46*, 165–171.

Rufiange, M., Dassa, J., Dembinska, O., Koenekoop, J. M., Little, J. M., Polomeno, R. C., et al. (2003). The photopic ERG luminance–response function (photopic hill): Method of analysis and clinical application. *Vision Research, 43*, 1405–1412.

Rufiange, M., Rousseau, S., Dembinska, O., & Lachapelle, P. (2002). Cone-dominated ERG luminance–response function: The photopic hill revisited. *Documenta Ophthalmologica, 104*, 231–248.

Seiple, W., & Holopigian, K. (1994). The 'OFF' response of the human electroretinogram does not contribute to the brief flash 'b-wave'. *Visual Neuroscience, 11*, 667–673.

Sieving, P. A. (1993). Photopic ON- and OFF-pathway abnormalities in retinal dystrophies. *Transactions of the American Ophthalmological Society, 91*, 701–773.

Sieving, P. A., Murayama, K., & Naarendorp, F. (1994). Push-pull model of the primate photopic electroretinogram: A role for hyperpolarising neurons in shaping the b-wave. *Visual Neuroscience, 11*, 519–532.

Ueno, S., Kondo, M., Niwa, Y., Terasaki, H., & Miyake, Y. (2004). Luminance dependence of neural components that underlies the primate photopic electroretinogram. *Investigative Ophthalmology and Visual Science, 45*, 1033–1040.

Valeton, J. M., & van Norren, D. (1983). Light adaptation of primate cones: An analysis based on extracellular data. *Vision Research, 23*, 1539–1547.

Wali, N., & Leguire, L. E. (1992). The photopic hill: A new phenomenon of the light adapted electroretinogram. *Documenta Ophthalmologica, 80*, 335–342.