



# The rod-driven a-wave of the dark-adapted mammalian electroretinogram



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## ABSTRACT

The a-wave of the electroretinogram (ERG) reflects the response of photoreceptors to light, but what determines the exact waveform of the recorded voltage is not entirely understood. We have now simulated the trans-retinal voltage generated by the photocurrent of dark-adapted mammalian rods, using an electrical model based on the *in vitro* measurements of Hagins et al. (1970) and Arden (1976) in rat retinas. Our simulations indicate that in addition to the voltage produced by extracellular flow of photocurrent from rod outer to inner segments, a substantial fraction of the recorded a-wave is generated by current that flows in the outer nuclear layer (ONL) to hyperpolarize the rod axon and synaptic terminal. This current includes a transient capacitive component that contributes an initial negative “nose” to the trans-retinal voltage when the stimulus is strong. Recordings in various species of the a-wave, including the peak and initial recovery towards the baseline, are consistent with simulations showing an initial transient primarily related to capacitive currents in the ONL. Existence of these capacitive currents can explain why there is always a substantial residual transient a-wave when post-receptor responses are pharmacologically inactivated in rodents and nonhuman primates, or severely genetically compromised in humans (e.g. complete congenital stationary night blindness) and *nob* mice. Our simulations and analysis of ERGs indicate that the timing of the leading edge and peak of dark-adapted a-waves evoked by strong stimuli could be used in a simple way to estimate rod sensitivity.

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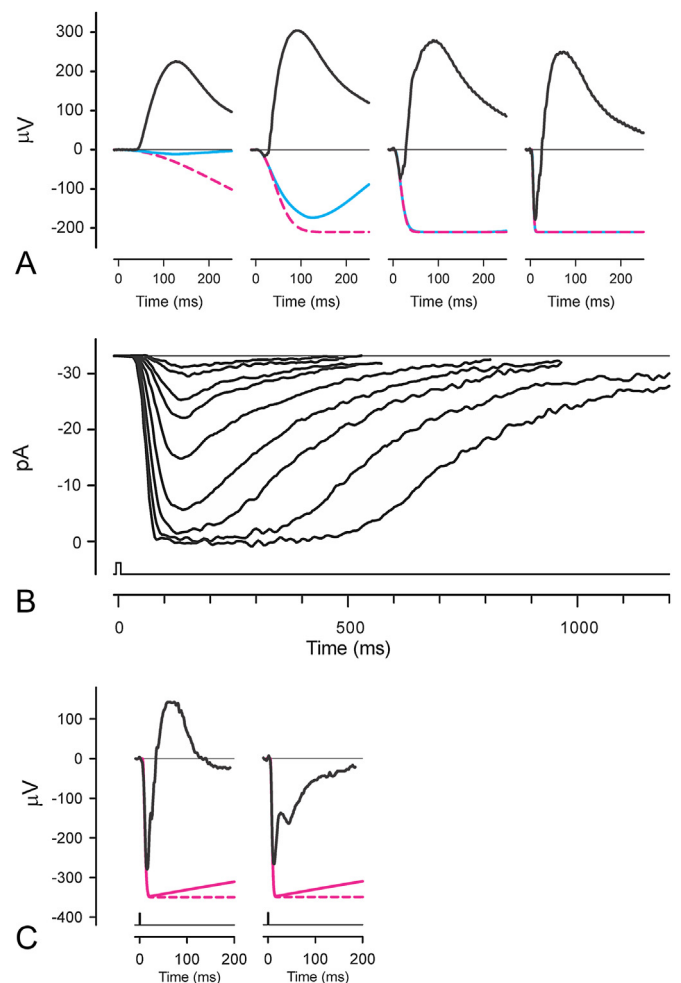
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## 1. Introduction

The initial negative deflection of the corneal electroretinogram (ERG) that appears when the light stimulus exceeds some minimal strength (Fig. 1A), was first designated the “A” deflection by Einthoven and Jolly (1908). They supposed that this deflection represented a brief transient component of the retinal response that was essentially complete before the onset of a slower and longer-lasting positive component that appeared in the ERG as the b-wave. Although alternative suggestions were made by subsequent investigators (e.g. Waller, 1909), this remained the generally accepted interpretation until Granit (1932) examined the effect of anaesthetics and various experimental interventions on the different “waves” (so named in Hartline, 1925) of the mammalian ERG. Granit’s (1932, 1933) observations of the differential effects of ether and circulatory and respiratory disturbance upon the ERG of decerebrate cats led him to conclude that the a-wave did not directly reflect the existence of an intrinsically brief negative response. Instead it resulted from the cancellation of the later part of a relatively prolonged negative component of short latency by a larger, more labile and slightly delayed positive component. Granit was unable to determine where the positive and negative components originated and simply referred to them as being generated by distinct processes that he called PII and PIII. While Granit’s work was accepted as establishing that the initial negative-going deflection of the ERG was provided by the leading edge of PIII, the retinal origin of PIII remained for some time a matter for speculation (Granit, 1947). Eventual resolution was achieved by recordings made with microelectrodes in retinas of intact cat eyes (see Brown, 1968) that confirmed that PIII was developed across the photoreceptor layers of the retina and by microelectrode recordings in rat retinal slices *in vitro* (Penn and Hagens, 1969) that demonstrated that the photocurrent originated in the rod outer segments. The intraretinal microelectrode studies in the intact cat eye also indicated a post-receptor origin for PII (b-wave) across the inner nuclear layer where bipolar cells are located.

Identification of the leading edge of the a-wave with onset of the photoreceptor response prompted Fulton and Rushton (1978), in a study of light and dark adaptation, to use the “slope” of a human subject’s ERG a-waves as an objective indicator of rod response and hence of rod sensitivity. However, based on the more specific assumption that the PIII component of the ERG is a direct reflection of rod photocurrent and would have the same timecourse, Hood and Birch (1990a) suggested that the slope of the a-wave would be more appropriately interpreted by taking into account the information that had by then become available about the photocurrent responses of primate rods recorded *in vitro* using a suction electrode technique by Baylor et al. (1984) (Fig. 1B). In particular, Hood and Birch showed how the slope of the a-wave depended on



**Fig. 1.** ERGs and photocurrents. A) ERGs (black lines) from anesthetized macaque to blue flash stimuli giving 10, 320, 2600, 55,000  $R^*/rod$ . Recording methods described by Robson et al. (2003); bandwidth of recordings was 0–300 Hz. Blue lines show simulations of a 3-stage filter model described in the text and dashed magenta lines show simulations of a basic Lamb and Pugh model. B) Suction electrode recordings (bandwidth 0–50 Hz) of the outer-segment photocurrent of a macaque rod to stimuli ranging from about 3 to 860  $R^*/rod$  (redrawn from Fig. 2 of Baylor et al., 1984). C) Recordings (bandwidth 0.1–300 Hz; stimulus 44.2  $cd\ s\ m^{-2}$ ) of ERGs of a normal human (left) and a patient with complete CSNB (right) redrawn from Miyake et al. (1994). Dashed magenta lines show the prediction of a Lamb and Pugh model fitted to the leading edge of the a-wave while the solid magenta line shows how this would have been recorded by a system with the same high-pass filter that was used for recording the ERGs.

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