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Mouse b-wave mutants

Machelle T. Pardue and

Rehabilitation Research and Development Center of Excellence, Atlanta VA Medical Center, 1670 Clairmont Road, Decatur, GA 30033, USA. Department of Ophthalmology, Emory University School of Medicine, 1365B Clifton Road NE, Atlanta, GA 30322, USA

Neal S. Peachey

Research Service (151W), Louis Stokes Cleveland VA Medical Center, 10701 East Boulevard, Cleveland, OH 44106, USA. Cole Eye Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA. Department of Ophthalmology, Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, 9500 Euclid Avenue, Cleveland, OH 44195, USA

Abstract

The b-wave is a major component of the electroretinogram that reflects the activity of depolarizing bipolar cells (DBCs). The b-wave is used diagnostically to identify patients with defects in DBC signaling or in transmission from photoreceptors to DBCs. In mouse models, an abnormal b-wave has been used to demonstrate a critical role of a particular protein in the release of glutamate from photoreceptor terminals, in establishing the structure of the photo-receptor-to-DBC synapse, in DBC signal transduction, and also in DBC development, survival, or metabolic support. The purpose of this review is to summarize these models and how they have advanced our understanding of outer retinal function.

Keywords

Electroretinogram; Retina; b-Wave; Depolarizing bipolar cell

Introduction

The electroretinogram (ERG) is a field potential that reflects the electrical response of the retina to a light stimulus. Under most recording conditions, the ERG is comprised of multiple components, each of which reflects the activity of distinct cellular generators. Because ERGs can be recorded using non-invasive procedures, they are used in a wide variety of applications to examine how experimental manipulation, genetic disease, and other factors impact retinal function [1].

The b-wave is a large amplitude component of the ERG, with a positive polarity when recorded at the corneal surface. In response to strong stimulus flashes, the b-wave follows the a-wave, which is initiated by the light-induced closure of ion channels along the photoreceptor outer segment [2]. For many years, the b-wave was thought to reflect the

Correspondence to: Neal S. Peachey.

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activity of inward rectifying K^+ (Kir) channels in Müller cells, evoked as a secondary response to bipolar cell activity [3–5]. More recent evidence indicates that the mammalian b-wave is generated primarily by bipolar cell activity, based on current-source density analysis of b-wave currents [6], the retention of the b-wave in mice lacking Kir4.1 expression [7], and pharmacological blockade of Kir channel activity by barium [7–10]. The b-wave has now been firmly linked to the activity of depolarizing bipolar cells (DBCs) [11–16]. As a consequence, b-wave abnormalities in conjunction with normal photoreceptor function provide insights into the molecular components that are involved in the cellular processes required to support b-wave generation [17]. As diagramed in Fig. 1, these include the pre-synaptic release of glutamate, structural properties of the photoreceptor-to-DBC synapse, and the DBC signal transduction cascade. The purpose of this review is to summarize mouse b-wave mutants that involve these molecules, as well as others that are not included on this diagram but impact b-wave generation due to a role in DBC development, metabolic support, survival, or some other physiological process. In reviewing the types of b-wave abnormalities that have been reported in mouse mutants, we will not encompass mouse models where the b-wave is reduced secondary to photoreceptor degeneration. The review is organized by the extent of b-wave reduction, which corresponds generally to whether a mutant involves a molecule involved in the pre- or post-synaptic aspects of the photoreceptor-to-DBC synapse, and notes how mouse b-wave mutants have played important roles in elucidating this initial stage of information transfer in the visual system and in the identification of human disease genes.

Typical ERG responses from wild-type (WT) mice

Figure 2 presents a series of ERGs recorded from a C57BL/6 WT mouse to strobe flashes obtained under dark-adapted (left) and light-adapted (right) conditions. At the lower stimulus levels, the dark-adapted ERG is dominated by the positive polarity b-wave, as the negative polarity a-wave component is hidden by the b-wave, which is of larger amplitude with similar kinetics [18–20]. The a-wave only becomes apparent when it precedes the b-wave at higher flash strengths. ERGs evoked by stimuli presented in the dark are dominated by activity of the rod pathway. Cone ERGs may be isolated by superimposing stimulus flashes upon a steady light-adapting field that desensitizes the rod pathway [21]. In the mouse, the overall amplitude of the cone ERG is substantially smaller than the dark-adapted ERG, and the response is dominated by the positive polarity b-wave across these and other stimulus conditions [22, 23]. The cone ERG b-wave nevertheless provides a measure of cone DBC activity [15].

Mouse mutants that lack b-waves due to post-synaptic defects

An extreme b-wave abnormality is the absence of this response component, referred to as a no b-wave (nob) ERG. Figure 3 compares WT responses with those of a *Trpm1*$^{-/-}$ mouse lacking the non-specific cation channel transient receptor potential melastatin 1 (TRPM1). At all flash levels, the dark-adapted *Trpm1*$^{-/-}$ ERGs lack the b-wave component [24–26]. As a consequence, the ERG is comprised of the initial a-wave followed by a slow negative polarity component. This component is slow PIII and reflects Kir4.1 channel activity in Müller glial cells [7, 27–30]. In comparison with the b-wave, higher light levels are required

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to evoke these responses (Fig. 3). Nevertheless, in these and other nob mice, the absence of the b-wave allows Müller cell function to be studied in vivo, by crossing an allele of interest to a nob background and examining the response properties of slow PIII [28, 31, 32].

A number of nob mutants with this phenotype have been described (Table 1), and the nob ERG phenotype has been instrumental in linking-specific proteins to post-synaptic proteins in the DBC signal transduction process. For example, mutations in the glutamate receptor, mGluR6, encoded by *Grm6* have a nob ERG phenotype [33], as do other mutants for *Grm6* (*Grm6*^{nob4} [34]; *Grm6*^{nob3} [35]). A nob ERG phenotype is seen in mouse mutants for several other genes involved in DBC signal transduction. These include *Trpm1* (Fig. 3) [24–26, 36]; *Nyx* [37, 38], which encodes nyctalopin, a leucine-rich repeat proteoglycan that appears to have restricted expression in DBCs and may play a key role in TRPM1 trafficking or stabilizing TRPM1 in the DBC dendritic terminal [39]; and *Gpr179* [40], encoding an orphan G-protein receptor that may interact with RGS (regulator of G-protein signaling) proteins [41]. A nob ERG phenotype has also been observed in mutants for several G-protein subunits located in the DBCs including *Gna01* [42, 43]; *Gnb5* [44], and *Gnb3* [45], implicating these proteins in DBC signal transduction (Fig. 1) [46, 47]. Because the DBC signal transduction process remains incompletely understood, ERG studies will continue to be important to confirm that deletion of a new candidate member of the DBC cascade leads to a nob ERG phenotype.

A remarkable feature shared by many nob models is that retinal anatomy is normal, including a normal OPL and INL as well as intact ribbon synapses between photoreceptors and DBCs and horizontal cells, although the expression of other proteins in the DBC cascade may be altered [48]. When a transgenic approach was used to deliver a wild-type copy of *Nyx* to *Nyx*^{nob} DBCs, the b-wave and inner retinal function were restored [38]. In Gregg et al. [38], the transgene constructed was driven by the GABAc ρ1 promoter, which is active early in development [49]. Further studies are needed to determine whether gene replacement will restore DBC function to an adult retina or in any of the other nob mouse models.

Like all G-protein coupled receptor cascades, the DBC signal transduction cascade needs to be deactivated. The expression of RGS7 and RGS11 in DBCs [50–54] suggested that these proteins may play a role in DBC signaling deactivation. When single mutants for *Rgs7* or *Rgs11* were examined, however, only modest ERG b-wave delays were observed [53, 55]. More recently, a nob ERG was noted in *Rgs7/Rgs11* double mutants [51, 56], indicating that RGS7 and RGS11 are functionally redundant in DBC deactivation.

A nob ERG phenotype has played an important role in the discovery of genes underlying the human condition complete congenital stationary night blindness (cCSNB). For example, the nob ERG phenotype of *Grm6*$^{-/-}$ mice [33] motivated the evaluation of GRM6 as a cCSNB gene [57, 58]. Similarly, the nob ERG phenotype of animal models for *Trpm1* [24–26, 59] and *Gpr179* [40] led to the discovery of *TRPM1* and *GPR179* mutations in patients with cCSNB [40, 60–63]. *NYX*, the first gene identified for cCSNB, was identified through gene mapping [64, 65]. To date, none of the other proteins listed in Table 1 have been implicated in human retinal disease.

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Mouse mutants with reduced b-waves

Gene defects at the photoreceptor terminal

Rod and cone photoreceptors use glutamate as the neurotransmitter [66, 67], which is released by photoreceptor terminals at a specialized ribbon synapse [68]. Glutamate release is mediated by calcium entry through slowly inactivating L-type voltage-dependent calcium channels (VDCCs; Fig. 1) [69]. The VDCC pore is defined by the α1 subunit, the activity of which is regulated by β, $\alpha_2\delta$, and γ subunits [70, 71]. Defects in VDCC subunits impair VDCC function and synaptic transmission [72], and b-wave reductions implicate a critical role of specific VDCC subunits in the control of glutamate release from photoreceptor terminals. Reduced b-wave amplitudes have been recorded in mice with defects in genes that encode VDCC subunits or calcium regulatory proteins (Table 2). Mutations in *CACNA1F*, encoding a photoreceptor-specific VDCC α_{1F} subunit, were identified in patients with incomplete congenital stationary night blindness (iCSNB) in whom ERG b-wave amplitudes are reduced but not absent [73–75]. Subsequently two *Cacna1f* mouse mutants have been described: $Cacna1f^{nob2}$ [76] and $Cacna1f^{-/-}$ [77]. Figure 4 compares ERGs of a $Cacna1f^{nob2}$ mutant with those of a WT mouse. The dark-adapted b-wave is greatly reduced, but not absent, as observed in the nob phenotype. The reduction in the dark-adapted b-waves is also noted in the $Cacna1f^{-/-}$ mouse [77]. The light-adapted ERGs are, however, distinct in these two models. While a measurable cone ERG is observed in $Cacna1f^{nob2}$ mutants (Fig. 4, right) [76], cone ERGs of $Cacna1f^{-/-}$ mice are more drastically reduced [77]. Both mutants display abnormalities in retinal architecture, including a thin OPL and ectopic neurites that elaborate from DBCs and horizontal cells [76, 77]. A similar phenotype is observed in mouse mutants for the β_2 (*Cacnb2*) [78] or $\alpha_2\delta_4$ (*Cacna2d4*) [79, 80] VDCC subunits, implicating these specific subunits in the VDCC used to control glutamate release at the photoreceptor terminal. The γ subunit used in the photoreceptor VDCC has not been identified.

In several instances, the b-wave reduction observed in a mouse mutant led to the identification of a human disease gene. For example, the ERG phenotype of $Cacna2d4^{C57BL/10}$ mice led to the evaluation of *CAC-NA2D4* as a candidate gene for iCSNB [81] and the identification of *CACNA2D4* mutations in patients with cone–rod dystrophy [82]. The reduced ERG b-wave phenotype of calcium binding protein 4-deficient ($Cabp4^{-/-}$) mice [83, 84] led to the identification of *CABP4* mutations in patients with iCSNB [85] or a cone–rod synaptic disorder [86, 87]. CACNB2 has not been linked to retinal disease, most likely because it is expressed in skeletal muscle and viable $Cacnb2^{-/-}$mice were only obtained when the protein was replaced in skeletal muscle using a transgenic approach [78].

A reduced b-wave is also seen in mutants for other proteins expressed at the photoreceptor terminal. These include the pre-synaptic ribbon component Bassoon [88] and CAST, a component of the pre-synaptic active zone [89]. In $Bsn^{-/-}$ mice, the absence of these pre-synaptic ribbon components is accompanied by ectopic neurites from horizontal and bipolar cells toward the outer nuclear layer and floating ribbons [90] *BSN* or *CAST* mutations have not been associated with human retinal disease.

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ERG b-waves are also reduced in patients with X-linked juvenile retinoschisis [91, 92], which is caused by mutations in retinoschisin (*RS1*). Figure 5 plots data obtained from a WT mouse with that of a $Rs1^{44TNJ}$ mutant that was identified in a ERG screen of a mutagenesis program [93]. Similar results have been reported for $Rs1^{-/-}$ mice [94, 95], and gene replacement has normalized the b-wave and anatomical defects associated with this model [96, 97]. The function of RS1 is not completely understood, but it may play a role in the retention of VDCC α subunits in the photoreceptor terminal membrane [98].

Gene defects in the dystrophin–glycoprotein complex

α and β dystroglycan, along with proteins that glycosylate dystroglycans, and several other members of the dystrophin–glycoprotein complex (DGC) play critical roles in skeletal muscle and the nervous system, and mutations in DGC elements underlie several complex disorders [99]. In the retina, dystroglycans are expressed in the endfeet of Müller glial cells, in photoreceptor ribbons, and on the photoreceptor cell membrane, connecting to DBCs (Fig. 1) [100–103]. Mutations of members of the DGC result in delayed and reduced b-waves (Table 3).

Glycosylation of α-dystroglycan by LARGE, the glycosyltransferase gene, is critical for the formation of a stable OPL [104]. Figure 6 contrasts ERGs of $Large^{vls}$ and WT mice. In comparison with WT, the dark- and light-adapted b-waves of the $Large^{vls}$ mutant are reduced in amplitude and have slow kinetics. A striking feature of the $Large^{vls}$ ERG phenotype is the slow onset of the dark-adapted b-wave. The ERG phenotype shown in Fig. 6 is also shared by $Large^{myd}$ mice, a second intragenic deletion within LARGE [104, 105] and by mouse mutants for other components of the dystroglycan complex (Table 3). A recent study of the $Pikachurin^{-/-}$ ribbon synapse indicates that DBC invaginations into photoreceptor terminals are abnormal, resulting in a larger gap between the pre-synaptic active zone and the post-synaptic membrane [103]. A larger synaptic gap could delay clearance of glutamate and thus result in a delayed b-wave onset. It remains to be determined whether other mutants for components of the dystroglycan complex have comparable structural abnormalities of the ribbon synapse.

ERG b-wave reductions were noted in some but not all patients with Duchenne muscular dystrophy which had DGC mutations [106–112]. Pillers and colleagues examined the Dmd^{mdx}; $Dmd^{Cv2–Cv5}$ series of dystrophin mouse mutants, and noted normal ERG b-waves in some (e.g., Dmd^{mdx}, $Dmd^{mdx–Cv5}$) and a selective b-wave reduction in $Dmd^{mdx–Cv3}$ mice, which lack expression of the Dp260 isoform [113–115]. This group subsequently defined a similar relationship between the mutation site and the b-wave phenotype in human patients [116].

Satz et al. [117] described a series of mouse models which lack dystroglycan expression in Müller cells or which express a mutant form of dystroglycan that lacked the C-terminal region. In each of these mutants, the ERG b-wave was reduced in amplitude [117]. Libby et al. [118] described b-wave reductions in mice lacking B laminin.

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Defects in development of the retinal vasculature

The retinal blood supply consists of a set of major arteries and veins that enter the eye from the optic disk and course across the vitreal face of the retina [119]. These vessels generate a series of smaller vessels that penetrate the retina and connect to a pair of capillary beds which flank the inner nuclear layer, the cell layer in which DBCs reside. The Norrin/Frizzled 4 signaling pathways have been implicated in retinal vascular development and diseases such as diabetic retinopathy and age-related macular degeneration [120]. Retinal vascular abnormalities and reduced b-waves (Fig. 7) are observed in mice lacking normal gene expression of Norrin (Ndp), a cystine knot protein [121–123]; Frizzled 4 (Fzd4), an integral membrane receptor [124, 125], or low-density lipoprotein receptor-related protein 5 (Lrp5), a Fzd4 co-receptor [126, 127]. When a conditional knockout approach was used to eliminate Fzd4 expression, elimination of Fzd4 in epithelial, but not neuronal cells, recapitulated the many aspects of the phenotype observed in the systemic knockout, including the reduced ERG b-wave [125]. Table 4 lists the mutants impacting development of the inner retinal vasculature, in which an ERG b-wave reduction has been documented.

Mouse mutant with hypernormal b-waves

The sections above have been organized around groups of mouse models involving proteins that are involved in a specific cellular process, such as DBC signal transduction, that when mutated or eliminated result in abnormal DBC function. A distinct ERG b-wave phenotype was reported in mice lacking PKCα, a protein that has long been targeted by immunohistochemistry to label rod DBCs [128]. As shown in Fig. 8, *PKCα*$^{-/-}$ mice have a large amplitude b-wave with an extremely slow recovery phase. The explanation for this unusual pattern is currently not known, but has been reported by two independent research groups [129, 130]. Consistent with the restriction of PKCα expression to rod DBCs [128], cone ERGs of *PKCα*$^{-/-}$ mice have normal response properties [129].

Mouse mutants for other retinal neurons or for bipolar cell development

While this review has mainly focused on alternations to the DBCs, loss of other inner retinal cells also impacts the b-wave. ERG b-wave reductions have been reported in transgenic mice that express an oncogene [131, 132] or a diphtheria toxin gene in horizontal cells [132]. Additionally, dark- and light-adapted b-waves were reduced in mice lacking the transcription factors *Bhlhb4*, which is required for rod DBC maturation [133], or *Math5*, which is required for development of retinal ganglion cells and of several classes of bipolar cell [134]. A selective reduction in the cone ERG b-wave, with normal dark-adapted b-waves, was noted in mice lacking Vsx1, a transcription factor required for cone bipolar cell development [135]. Finally, a nob ERG phenotype is observed in mice in which DBCs have been eliminated due to transgenic expression of an oncogene [136]. A similar ERG phenotype is seen in mutants for *Cpe*, encoding carboxypeptidase E [137]. A remarkable feature of the *Cpe* mutant phenotype is that it is age-related. The b-wave is retained in young *Cpe*$^{fat/fat}$ mice and is only lost when mice reached 6 months of age [137]. The underlying mechanism for this age-related abolition of the b-wave remains to be determined.

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Conclusions

DBCs play an instrumental role in transmitting the visual signal initiated by photoreceptors centrally. The ability to monitor DBC activity via the ERG b-wave has greatly facilitated our understanding of the mechanisms of DBC signal transduction/regulation and the processes that are required for DBC development and for maintaining normal DBC function. As is the case in many other biomedical fields, mouse models have been instrumental to much of this progress. It is likely that analysis of ERG b-waves of mouse mutants will yield further insights into DBC physiology.

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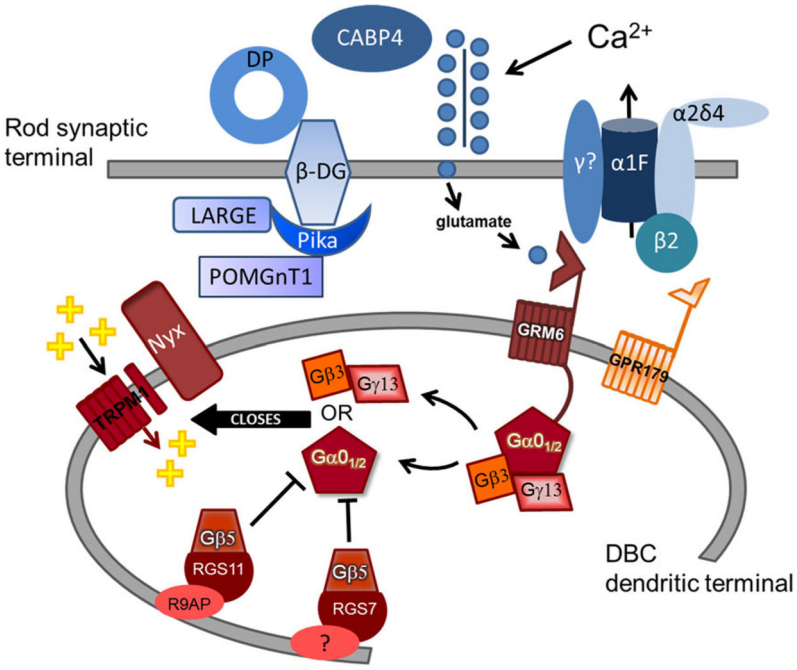

Fig. 1.

Diagram of molecules required for normal signaling between photoreceptors and DBCs. Pre-synaptic proteins (*blue symbols*) include the L-type voltage-dependent calcium channel composed of α1F, β2, γ, and α2δ4 subunits and the dystrophin–glycoprotein (DG) complex consisting of β subunit, the glycosyltransferase gene LARGE, pikachurin (Pika), Protein *O*-mannose beta1,2-*N*-acetylglucosaminyltransferase 1 (POM-GnT1), and dystrophin (DP). Post-synaptic proteins (*red symbols*) include metabotropic glutamate receptor 6 (GRM6), the orphan G-protein receptor GPR179, members of the G-protein regulating complex (Gβ5, RGS7, RGS11, and R9AP), G-protein subunits Gβ3, Gγ13, $G\alpha 0_{1/2}$, the transient receptor potential melastatin 1 (Trpm1) cation channel, and nyctalopin (Nyx). Mutants for post-synaptic proteins lack the ERG b-waves, while this response component is reduced but retained in mutants for pre-synaptic proteins

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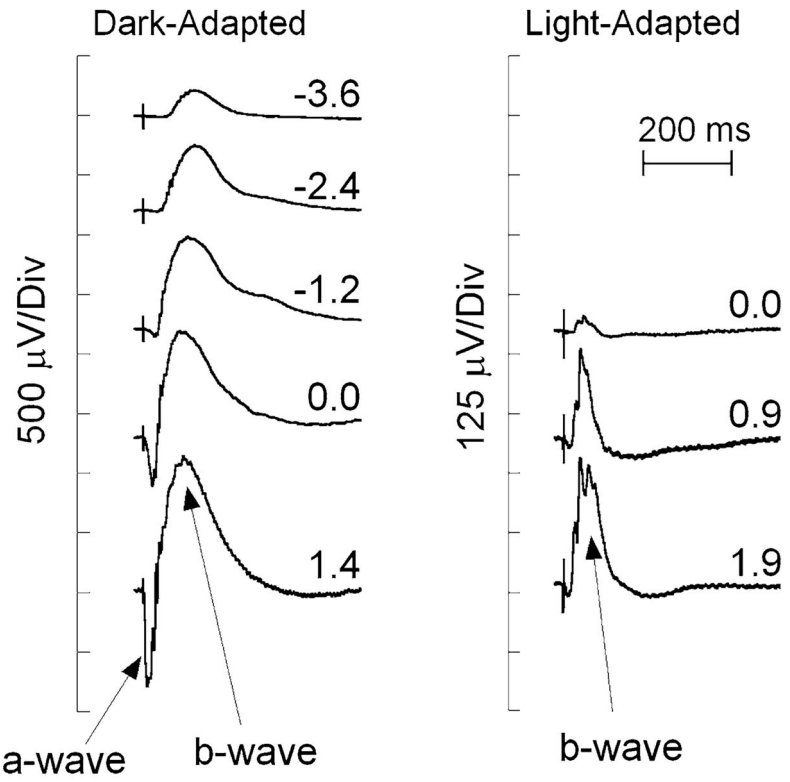

Fig. 2.

Representative ERGs recorded from the corneal surface of a WT mouse in response to strobe flash stimuli presented to the dark-adapted (*left*) or light-adapted eye (*right*). The b-wave is seen as a cornea positive potential, which increases in amplitude with increasing flash strength, indicated by the values next to each waveform, in log cd s/m^2

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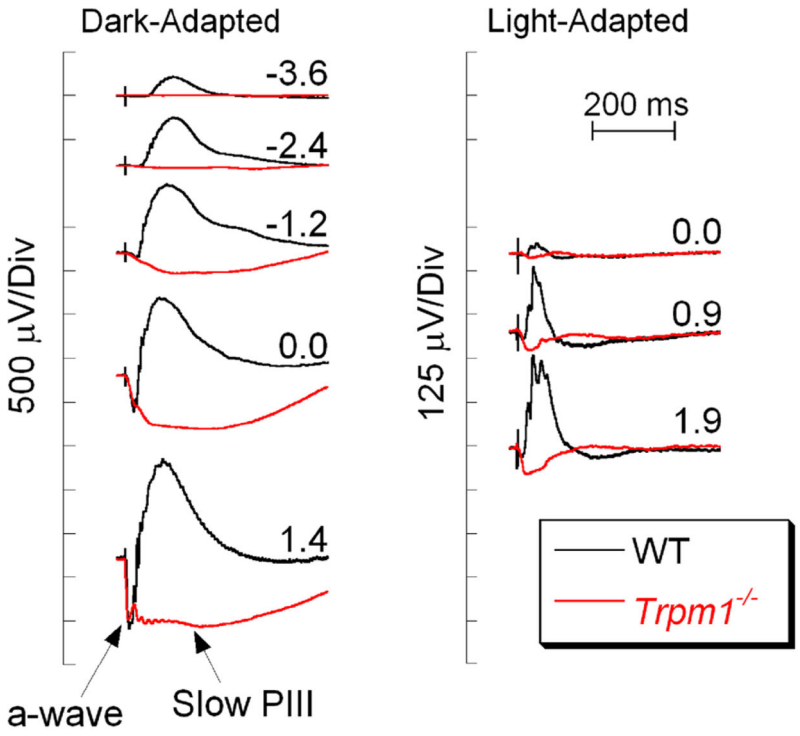

Fig. 3.

Comparison of WT and *Trpm1*$^{-/-}$ ERGs. WT ERGs are replotted from Fig. 1. The absence of the b-wave reveals slow PIII in the *Trpm1*$^{-/-}$ responses. Flash strength (log cd s/m^2) is indicated by the *values* next to each pair of waveforms

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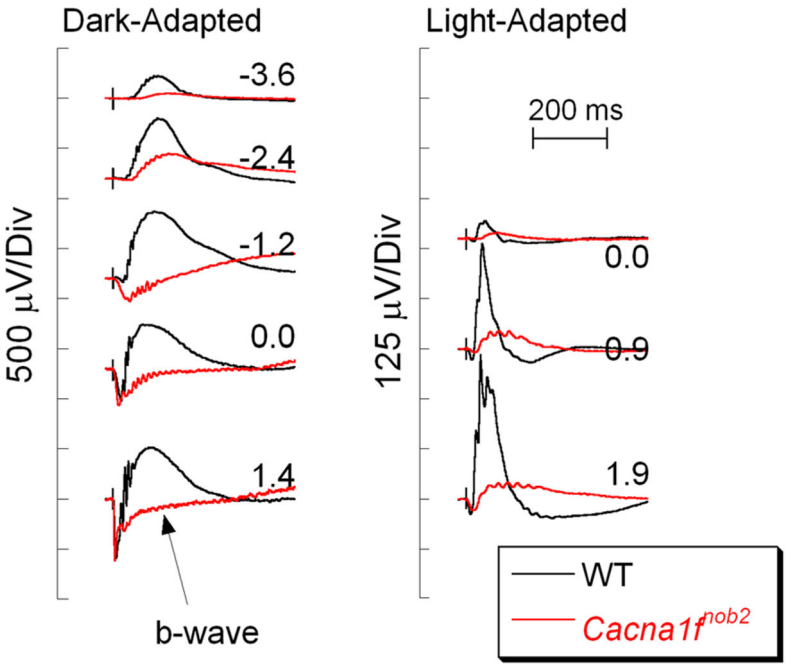

Fig. 4.

Comparison of WT (*black*) and *Cacna1f*^{nob2} (*red*) ERGs. Note that the b-wave is reduced but not absent in the *Cacna1f*^{nob2} responses. Flash strength (log cd s/m^2) is indicated by the *values* next to each pair of waveforms

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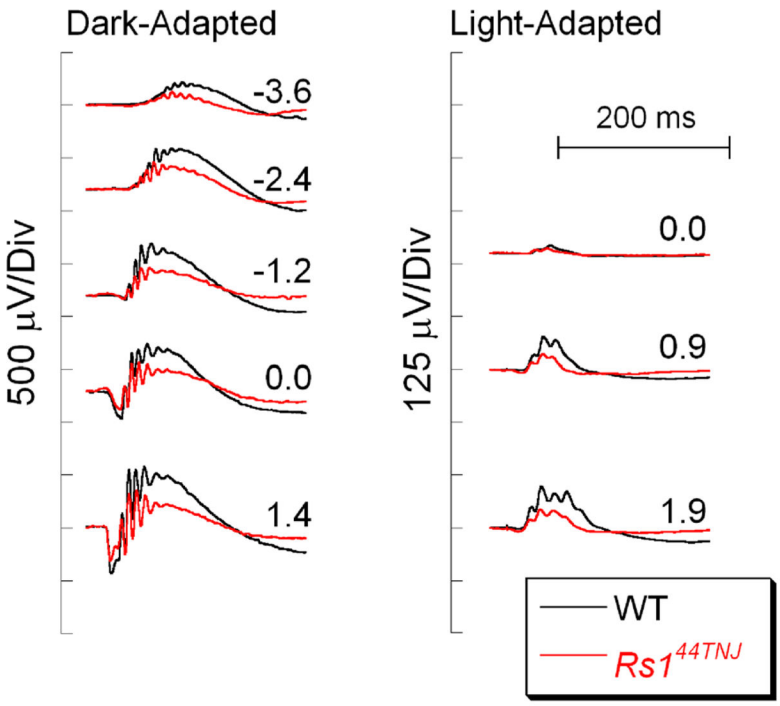

Fig. 5.

Comparison of WT (*black*) and *Rs1*^{44TNJ} (*red*) ERGs. Note that ERG b-waves are reduced in the *Rs1*^{44TNJ} mutant. Flash strength (log cd s/m^2) is indicated by the *values* next to each pair of waveforms

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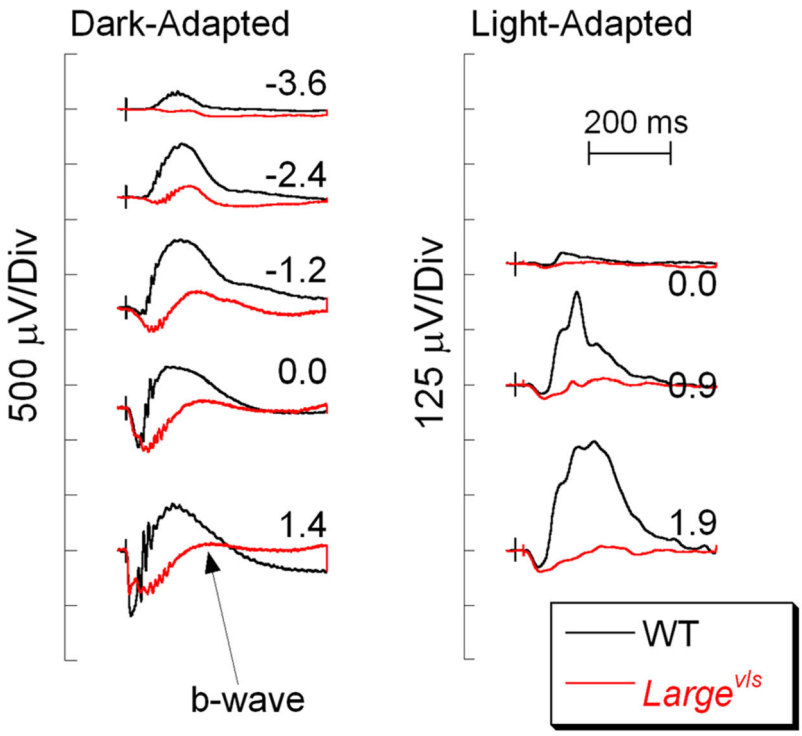

Fig. 6.

Comparison of WT (*black*) and *Large*^{vls} (*red*) ERGs. Note that the b-wave is reduced but not absent in the *Large*^{vls} responses, and has a slow onset. Flash strength (log cd s/m^2) is indicated by the *values* next to each pair of waveforms

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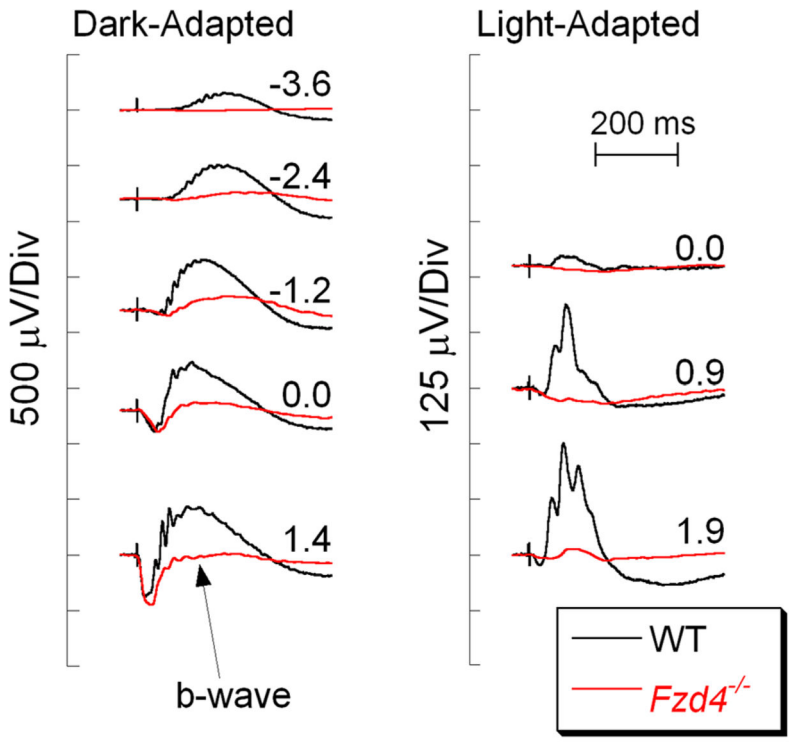

Fig. 7.

Comparison of WT (*black*) and *Fzd4*$^{-/-}$ (*red*) ERGs. Note that the b-wave is reduced but not absent in the *Fzd4*$^{-/-}$responses. Flash strength (log cd s/m^2) is indicated by the *values* next to each pair of waveforms

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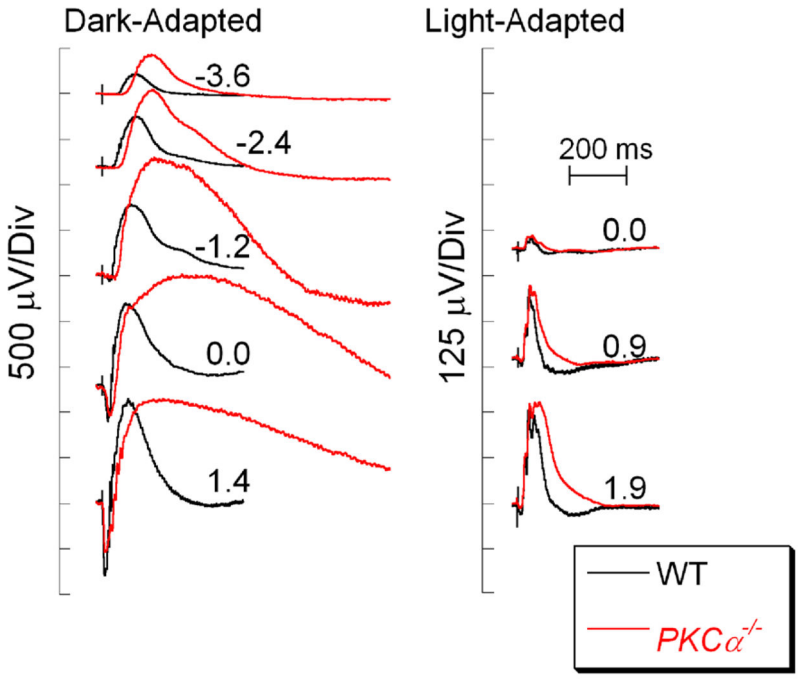

Fig. 8.

Comparison of WT (*black*) and *PKCα*$^{-/-}$ (*red*) ERGs. Note that the dark-adapted *PKCα*$^{-/-}$ b-waves are larger in amplitude and have a very prolonged time course and recovery. Flash strength (log cd s/m^2) is indicated by the *values* next to each pair of waveforms

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Table 1

Mouse no b-wave mutants for DBC signal transduction/modulation

Allele	Type of mutation	References
Gna01$^{-/-}$	Knockout	[42, 43]
Gnb3$^{-/-}$	Knockout	[45]
Gnb5$^{-/-}$	Knockout	[44]
Gpr179^{nob5}	6.5-kb insertion	[40]
Grm6$^{-/-}$	Knockout	[33]
Grm6^{nob3}	65-bp insertion	[35]
Grm6^{nob4}	Point (S207P)	[34]
Nyx^{nob}	85-bp insertion	[37, 38]
RGS7$^{-/-}$/*RGS11*$^{-/-}$	Double knockout	[51, 56]
Trpm1$^{-/-}$	Knockout	[24–26]
Trpm1^{tvrm27}	Point (A1068T)	[36]

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Table 2

Pre-synaptic mouse mutants with reduced b-waves

Allele	Type of mutation	References
Cacna1f$^{-/-}$	Knockout	[77]
Cacna1f^{nob2}	Insertion	[76]
Cacna2d4$^{-/-}$	Premature stop (c.2367insC)	[79, 80]
Cacnb2$^{-/-}$	Knockout	[78]
Cabp4$^{-/-}$	Knockout	[83]
Bassoon$^{-/-}$	Knockout	[88]
CAST$^{-/-}$	Knockout	[89]
Rs1$^{-/-}$	Knockout	[94, 95]

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Table 3

Mutants of the dystroglycan complex with reduced and delayed b-waves

Allele	Type of mutation	References
B laminin$^{-/-}$	Knockout	[118]
Large^{myd}	Spontaneous deletion	[104, 105]
Large^{vls}	Premature stop at aa37	[32, 104]
Dmd$^{mdx-Cv3}$	Point mutation, intron 53	[113–115]
Nestin-CRE/*DG*$^{-/-}$	Müller cell-specific knockout of dystroglycan	[117]
GFAP-CRE/DG$^{-/-}$	Müller cell-specific knockout of dystroglycan	[117]
DGβcyt/βcyt	Transgene lacking cytoplasmic region of β-dystroglycan	[117]
POMGnT1$^{-/-}$	Knockout	[138]
Pikachurin$^{-/-}$	Knockout	[139]

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Table 4

Mutants impacting inner retinal vascularization

Allele	Type of mutation	References
Fzd4$^{-/-}$	Knockout; conditional knockout	[125]
Lrp5$^{-/-}$	Knockout	[126]
Lrp5^{r18}	Single nucleotide insertion	[126, 127]
Ndp$^{Y/-}$	Knockout	[121–123]