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ORIGINAL RESEARCH ARTICLE

Comparison between albino and pigmented rabbit ERGs

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Abstract

Background Pigmented and albino rabbits are commonly used in visual research; however, the lack of pigment in the eyes may affect retinal responses. Here, we compare and describe the differences of retinal function between pigmented (English Butterfly) and albino (New Zealand) rabbits.

Methods Electroretinograms were recorded in pigmented and albino rabbits in the dark-adapted eye, in the light-adapted eye and for four temporal frequencies in the light-adapted eye. The implicit time and amplitude of the a- and b-waves were analyzed, as well as the amplitude and phase of the first harmonic component of the photopic flicker response.

Results Albino rabbits presented significantly larger amplitudes for both a- and b-waves at all intensities and frequencies. The intensity–response function of the scotopic b-wave also showed that the albino retina is more sensitive than the pigmented retina and the larger flicker amplitudes found in the albino group also revealed post-receptoral changes specifically related to cone pathways.

Conclusions The larger amplitude of albino receptoral and post-receptoral activities might be attributed to greater availability of light due to scatter and reflection at the retinal layer, and as the differences in response amplitudes between the groups increase with flicker frequency, we suggest that ON bipolar cells recover faster in the albino group, suggesting that this might be a mechanism to explain the higher temporal resolution for albinos compared to the pigmented group.

Keywords Rabbit · Albino · Pigmented · Retina · Electroretinogram

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Introduction

Rabbits are the most common experimental models used for preclinical safety evaluation of ocular drug toxicity as eye anatomy of human and rabbit is similar, and rabbits are docile and easy to handle [1–3]. In addition, intravitreal volume and drug clearance values do not lead to significant pharmacokinetic differences between rabbit and human [4, 5, 6].

Although albinism is associated with ocular and visual abnormalities, non-pigmented rabbits have been extensively used in preclinical studies on ocular pharmacology. The lack of pigment affects the retinal

pigment epithelium (RPE) that is crucial for the light absorption [7, 8], the transport of nutrients and metabolites [9, 10], photoreceptor outer segment renewal process [11], growth factors secretion [12, 13] and visual cycle [14], and these alterations may lead to different electrophysiological and morphological results found for albino and pigmented mice [15], rats [16, 17] and humans [18–20]. In the case of rabbits, only one study published in the 1970s compared and described the scotopic responses of the electroretinogram (ERG) between albino and pigmented [21]. Photopic functions, however, have not been examined. Here we expanded the functional evaluation of the normal retina of albino and pigmented rabbits to include, in addition to scotopic responses, an analysis of photopic function and of temporal resolution.

Methods

Two different breeds of rabbits were studied: 43 pigmented English Butterfly and 57 albino New Zealand animals were treated in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. All animals were male and about the same age (5–6 months). Experiments were approved by the Committee for Ethics in Animal Research, Instituto de Psicologia, Universidade de São Paulo, São Paulo, Brazil.

Light stimulation provided by a Ganzfeld LED stimulator (Q450 SC Roland Consult, Germany) was controlled by a computerized system (RetiPort, Roland Consult, Germany). The ERG signals were acquired and recorded with the same system, amplified $100,000\times$ and filtered between 0.3 and 300 Hz. Full-field ERG was performed simultaneously in both eyes, and the responses were recorded using a corneal lens bipolar electrode (GoldLens, Doran Instruments Inc., Littleton, MA) and a ground electrode (model E5; Grass Technologies, West Warwick, RI) placed on the ear.

Animals were housed in individual cages under 12/12-h light–dark cycle with free access to water and food. Before ERG sessions, animals were dark-adapted during 30 min. The rabbits were anaesthetized with intramuscular injection of 35 mg/kg ketamine hydrochloride (Ketamina; Agener, São Paulo, Brazil) and 5 mg/kg xylazine hydrochloride

(Calmiun; Agener, São Paulo, Brazil). Pupils were dilated with topical 0.5% tropicamide (Mydriacyl; Alcon, São Paulo, Brazil), the eyes were topically anesthetized with 0.5% proxymetacaine hydrochloride (Anestalcon; Alcon, São Paulo, Brazil) and protected with 1% methylcellulose gel (Metilcelulose 1%; Ophthalmos, São Paulo, Brazil).

The dark-adapted protocol modified from the International Society for Clinical Electrophysiology of Vision (ISCEV) [22], started after 30 min of dark adaptation. To minimize the potential bleaching of rods, inter-stimulus intervals (IFIs) were increased as the stimulus luminance was elevated. Thus, the sequence of the ERG protocol was:

1. 10 flashes at 0.00095 cd s/m^2 with 5 s IFIs;
2. after 10 s, 6 flashes at 0.0095 cd s/m^2 with 5 s IFIs;
3. after 20 s, 6 flashes at 0.095 cd s/m^2 with 10 s IFIs;
4. after 1 min, 6 flashes at 0.95 cd s/m^2 with 10 s IFIs.

The light-adapted protocol started following 2 min of light adaptation (25 cd/m^2) and consisted of:

1. 6 flashes at 9.5 cd s/m^2 with 5 s IFIs on a 25 cd/m^2 background (white light),
2. flickering light of 9.5 cd s/m^2 presented on a 25 cd/m^2 background (white light) at four different temporal frequencies: 12, 18, 24 and 30 Hz.

The a- and b-wave amplitudes and implicit times of the ERGs were measured. The a-wave amplitude peak was measured from the baseline to the first minimum amplitude after light stimulus onset. The a-wave implicit time was measured from flash onset to the a-wave peak. The b-wave amplitude was measured from the a-wave trough to the b-wave peak amplitude. The b-wave implicit time was measured from stimulus onset to the b-wave peak. The b-wave amplitudes were fitted by the Naka–Rushton equation:

$$V = V_{\max} \frac{\text{In}}{k^n + I^n},$$

where $V_{\max}$ is the b-wave saturating amplitude, l is the light intensity, k is the semi-saturation constant and n is the slope of the function, representing the dynamic range of the measured wave [23, 24].

Statistical analysis

Amplitude and implicit time are expressed as mean ± standard deviation. Statistical analyses were carried out using repeated-measures ANOVA and Fisher's least significant difference test as post hoc test. Parameters from Naka-Rushton equation of the b-wave intensity–response function were analyzed with one-way ANOVA and paired two-tailed t test with Bonferroni correction for the number of comparisons among treatment groups and intervals. $p < 0.05$ was considered statistically significant, and in results, one asterisk indicates $p < 0.001$ and two asterisks $p < 0.0001$. A fast Fourier transform (FFT) analysis was performed in the photopic flicker response, and results were expressed as amplitude and phase of the first harmonic.

Dark and light adaptation test

To test and validate the dark and light adaptation of our protocol, we compared the scotopic responses of six albino and six pigmented rabbits after 30 min and 6 h of dark adaptation as well as we compared the photopic responses after 2 and 10 min of light adaptation.

Results

Scotopic ERG responses

Scotopic ERG parameters from albino and pigmented rabbits were compared. Figure 1 shows representative scotopic ERGs from albino and pigmented rabbits. It is possible to observe a- and b-wave amplitudes and implicit time as a function of flash intensities. The a-wave is not detectable or very small in amplitude at the lowest intensities, and the $V\log I$ plot demonstrates good approximation to linearity for both the pigmented ($R^2 = 0.99$) and albino ($R^2 = 0.98$) animals, from the luminance levels where a-wave was detected (> 0.095 cd s/m^2). The b-wave rises with intensity since the lowest value, but the rise of the $V\log I$ function is not linear, especially for the albino rabbit. The function increases to a peak followed by a plateau in the rod-dominated part of the function and proceeds to grow linearly thereafter, at the higher intensities, in a combination of cone and rod systems.
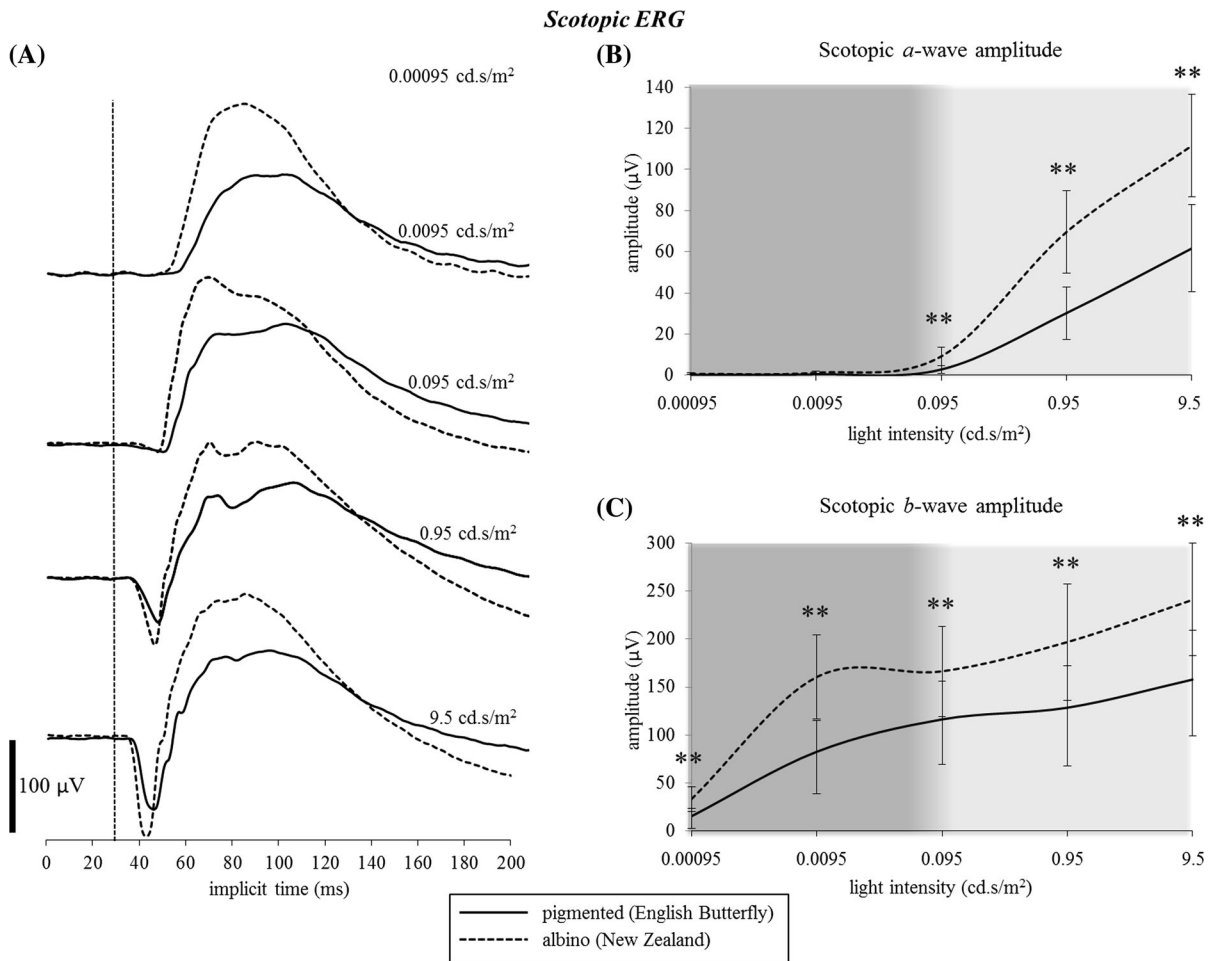
Statistical analysis shows that albino rabbits presented significantly larger a-wave amplitudes than pigmented at four of the five intensities presented (9.5 to 0.095 cd s/m^2 $p < 0.0001$ and 0.0095 cd s/m^2 $p < 00001$) and faster a-wave at 0.95 ($p = 0.004$) and 9.5 cd s/m^2 ($p = 0.0001$) (Fig. 1b). Albino rabbits also presented larger b-wave amplitudes at all flash intensities tested ($p < 0.0001$) (Fig. 1c) and faster b-wave at 0.00095 ($p = 0.0001$).

The dark-adapted b-wave $V\log I$ function was analyzed by fitting it to the Naka–Rushton equation (Fig. 2). Table 1 shows the resulting parameters. In albino rabbits, b-wave saturating amplitude ($V_{\max}$) was higher than in pigmented rabbits ($p < 0.0001$), as well as the slope of the function (n), representing the retinal sensitivity ($p < 0.002$). No differences were found comparing the semi-saturation constant (k) between the two groups.

Dark adaptation test

Two different dark adaptation durations were compared. Figure 3 shows the a- and b-waves mean implicit times and amplitudes obtained as a function of light intensity (log cd s/m^2) for albino and pigmented rabbits, after 30 min and 6 h of dark adaptation. No differences between adaptation times in albino or pigmented rabbits were found for implicit time or amplitude at any of the intensities.

A comparison between results from albino and pigmented rabbits for the two adaptation times shows that albino rabbit ERGs had statistically significant shorter implicit times at all light intensities. Their ERGs also had larger a-wave amplitudes than those of pigmented animals, with statistically significant difference at one light intensity but not at the other four (Fig. 4). For the b-wave, there was a statistical difference at four of five intensities used after 6 h of dark adaption. However, no statistical difference between ERGs of the two species was found after 30 min of dark adaptation. This difference between this experiment, with $n = 6$ animals in each group, and the previous data (Fig. 2), with pigmented ($n = 43$) and albino ($n = 57$) rabbits, might be due to the number of animals.

Scotopic ERG

(A)

0.00095 cd.s/m²

0.0095 cd.s/m²

0.095 cd.s/m²

0.95 cd.s/m²

9.5 cd.s/m²

100 μV

(B) Scotopic *a*-wave amplitude

(C) Scotopic *b*-wave amplitude

pigmented (English Butterfly)
albino (New Zealand)

Fig. 1 a Representative scotopic electroretinogram recordings for pigmented (English Butterfly) and albino (New Zealand) rabbits. **b** Comparisons of scotopic a-wave amplitudes between pigmented and albino rabbits. **c** Comparisons of scotopic b-wave amplitudes between pigmented and albino rabbits. Vertical bars = SD, $*p < 0.0001$ and $**p < 0.00001$. The background is gray along the intensities that comprise the rod-dominated part of the function and white in cone-dominated part of the function

Photopic ERG responses

Representative photopic ERGs of albino and pigmented rabbits and the mean amplitudes for both groups are shown in Fig. 5. Results show an increase in a- and b-wave amplitudes as well as faster b-wave for albino rabbits when compared to pigmented rabbits.

Light adaptation test

Two different durations of light adaptation were compared: 2 and 10 min. No differences between adaptation times in albino or pigmented rabbits were found for a- and b-wave implicit time or amplitude for albino (Table 2) and pigmented rabbits (Table 3).

Flicker responses

Flicker ERGs were also compared between albino and pigmented rabbits. Figure 6 shows representative recordings of photopic ERGs in response to flicker at four different temporal frequencies (12, 18, 24 and 30 Hz). The albino group presented a larger ERG amplitude when compared with pigmented, and as expected, the higher the temporal frequency of the stimulus, the larger the difference between groups.
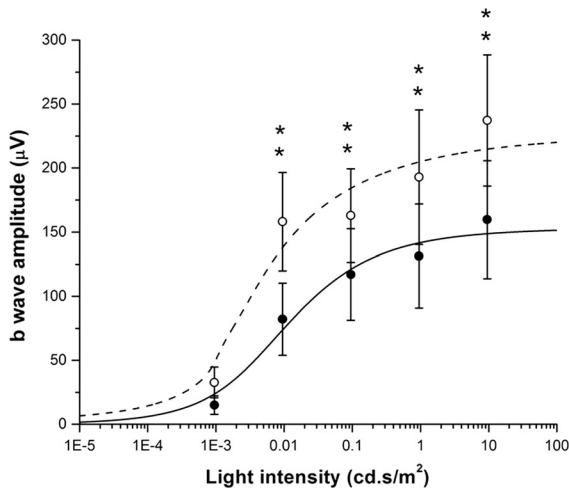
Fig. 2 Mean b-wave amplitudes for albino (open circles) and pigmented rabbits (filled circles) as a function light intensity. Dotted and continuous functions correspond to albino and pigmented rabbits data fits, respectively, using the Naka–Rushton equation; vertical bars = SD; **$p < 0.00001$

Amplitude and phase of the first harmonic component of the photopic flicker were analyzed through the fast Fourier transforms and compared between albino and pigmented group. Figure 7 shows the mean amplitudes and phases, along with respective standard deviations of the first harmonic at 12, 18, 24 and 30 Hz.

The statistical analysis showed significant differences in the flicker amplitudes at 18, 24 and 30 Hz ($p < 0.0001$), once again confirming the larger amplitude of the albino group ERG. In addition, our results indicate a significant increase in ERG amplitude with increase in stimulus temporal frequency for the albino group, while the reverse is seen in pigmented rabbits. The amplitude increase at 24 and 30 Hz compared to 12 and 18 Hz in the albino group is statistically significant ($p < 0.0001$). Conversely, the amplitude reduction at 30 Hz compared to the other temporal frequencies is statistically significant in the pigmented group ($p < 0.0001$).

The analysis also showed a phase difference over the four frequencies tested ($p < 0.001$).

Discussion

In this study, we analyzed the differences in visual function measured by the ERG in albino and pigmented rabbits, and our results suggest that the differences found may be related to the degree of pigmentation of the eye.
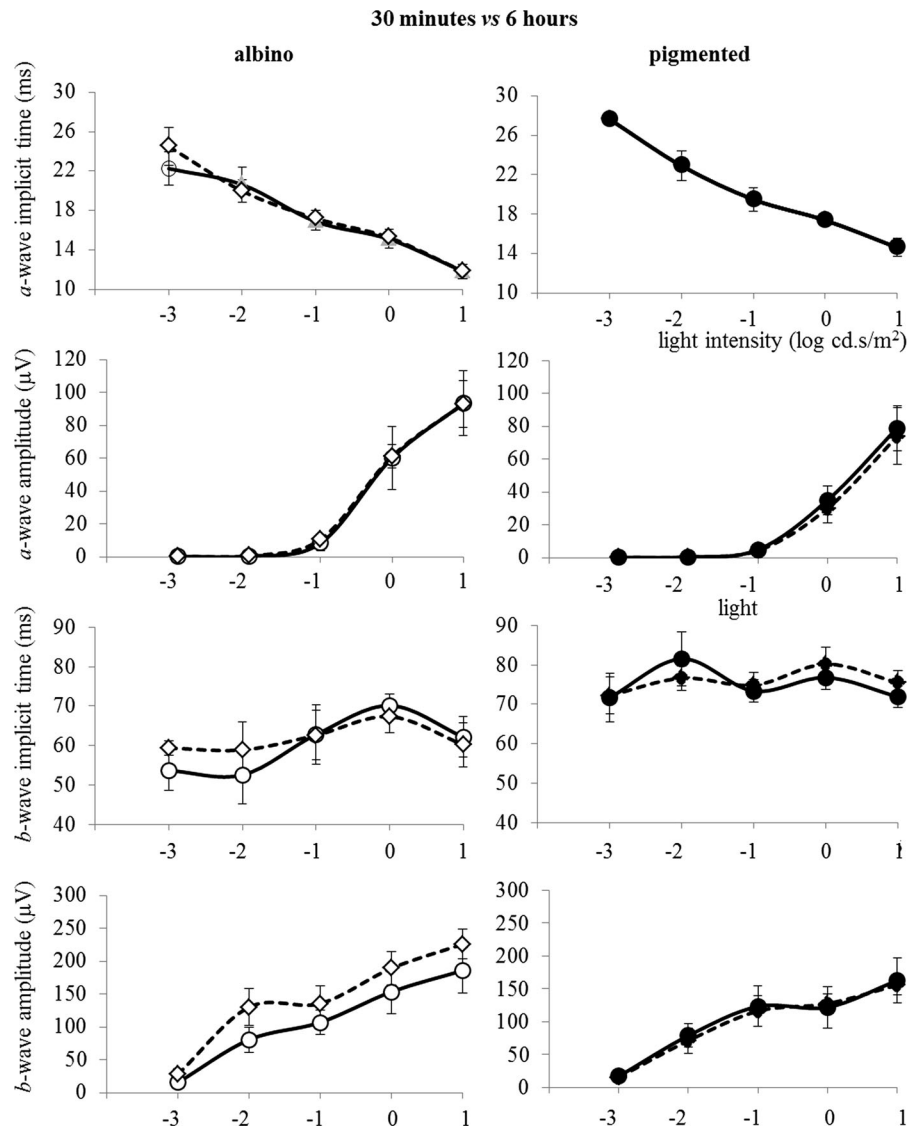
The ERGs of albino rabbits presented larger amplitude in scotopic, photopic and flicker responses. The differences between pigmented and albino rabbits observed in all scotopic flash intensities for both a- and b-waves suggest that cone, rod and post-receptoral responses are larger in albino rabbits. The larger amplitude of albino receptoral and post-receptoral activities might be attributed to greater availability of light due to scatter and reflection at the retinal layer, and as the differences in response amplitudes between the groups increase with flicker frequency, we suggest that ON bipolar cells recover faster in the albino group and this might be a mechanism to explain the higher temporal resolution for albinos compared to the pigmented group. Furthermore, the results of Table 1 showed that both K values are not significantly different from each other; however, the albino sigmoid curve shifted to the left (Fig. 2) may indicate that New Zealand animals present higher retinal sensitivity than English Butterfly [24, 25].

Some studies with rabbits also support our findings. By overlapping the a-wave of albino and pigmented rabbits, Reuter showed that the b-wave response curves coincided only at lower intensities, not at higher intensities [21]. Moraes Filho and colleagues used a portable handheld system to show that albino

Table 1 Parameters obtained from the Naka–Rushton equation for albino and pigmented rabbits in scotopic ERG (mean ± standard deviation)

	Albino (mean ± SD)	Pigmented (mean ± SD)	p level
V_{max} (μV)	227.0 ± 58.9	153.7 ± 45.1	< 0.0001
K (cd s/m^2)	0.075 ± 0.410	0.077 ± 0.390	0.9812
N	1.42 ± 0.73	1.90 ± 0.23	0.0276

Fig. 3 Comparisons of a- and b-waves amplitudes and implicit times between 30 min (circles) and 6 h (diamonds) of dark adaptation. On the left, we can observe data from albino rabbits (white markers) and, on the right, from pigmented rabbits (black markers). Vertical bars = SD


rabbits present larger amplitudes and faster responses than pigmented animals (Chinchila rabbits) [26]. Odom and colleagues studied the effect of acetazolamide in pigmented and albino rabbits under dark and light adaptation. The results of control albinos presented larger responses for dark and light conditions (average 230 and 130 µV consecutively), when compared with pigmented (average of 180 and 80 µV consecutively). Although the authors evaluated the effect of the drug in both breeds, the ERG differences between albinos and pigmented were not mentioned in the article [27].

Others animals such as guinea pig also presented similar results, which show that albino subjects present higher a- and b-wave amplitudes and shorter implicit time than pigmented strains as well as reduced semi-saturation constant and increased slope [28, 29]. Human studies with children and adults also showed that albinos present larger ERG amplitudes and shorter implicit time for both a- and b-waves when compared with pigmented individuals [18–20, 30, 31].

Albino subjects present larger ERGs when compared with pigmented, but they present worse visual conditions, as previously reported in humans with

Fig. 4 Comparisons of a-
and b-waves amplitudes and
implicit times between
albino (white markers) and
pigmented rabbits (black
markers) in different periods
of dark adaptation: 30 min
(circle) and 6 h (diamond).
Vertical bars = SD,
*$p < 0.01$ and **$p < 0.001$
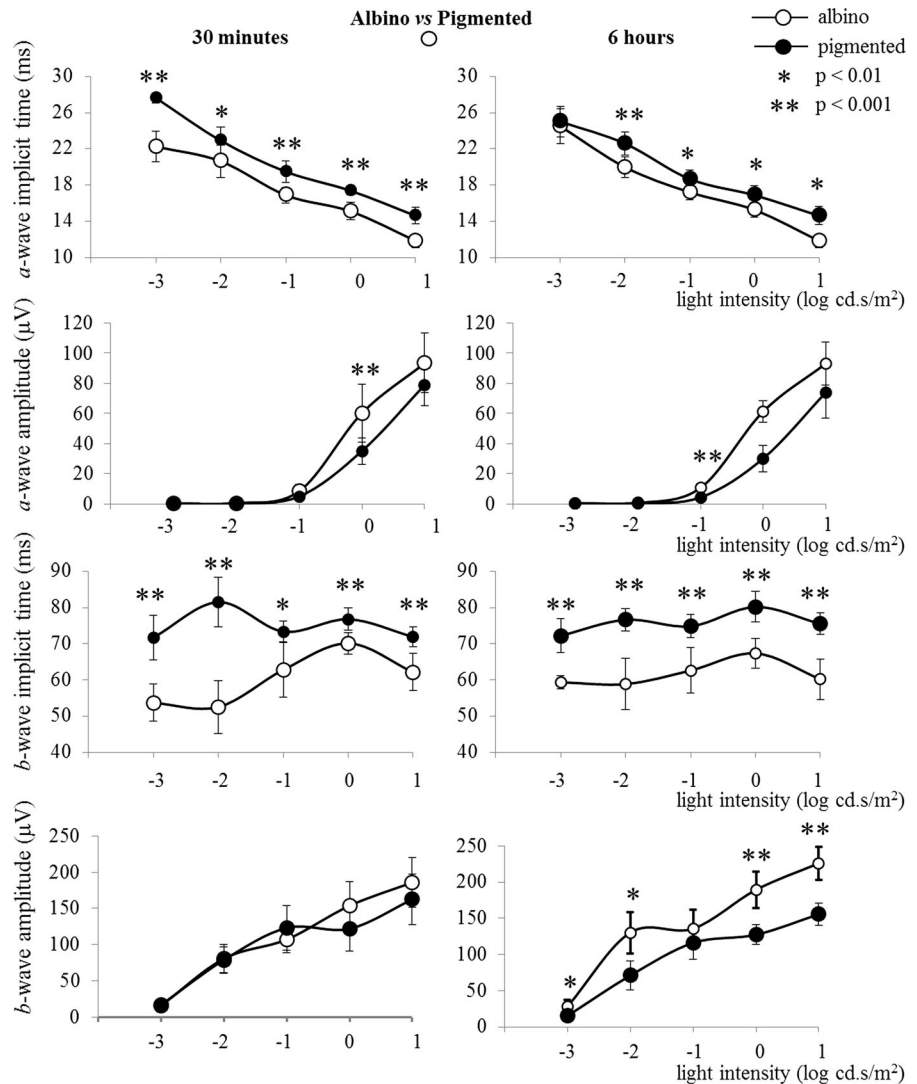
behavioral, anatomic and electrophysiological methods [32–35].

Clinical analyses also showed an inverse relationship between the degree of hypopigmentation and the level of visual acuity. This reduction in vision is a result of a variety of factors: refractive errors, foveal hypoplasia, nystagmus and amblyopia. Electrophysiology also showed that albino humans present alterations not only in the retina but also in higher levels of the visual pathway, as detected through the visual evoked potential (VEP), which showed interhemispheric latency and amplitude asymmetry, indicating the disorganization of the optic fibers [34, 35].

However, in contrast to our results and the studies cited above, some pigmented rodents have been reported to present larger amplitudes compared to albinos. Heiduschka and Schraermeyer compared ERGs from albino and pigmented rats and showed that the latter presented larger b-wave responses for both scotopic and photopic stimuli and larger a-wave amplitudes at bright light intensities when compared with albino rats [16]. Balkema also showed that albino mice and rats have elevated dark-adapted thresholds compared to pigmented animals by single-unit recordings from the superior colliculus [17]. The smaller amplitudes found in these albino rodents can be

Fig. 5 a Representative photopic ERGs for pigmented (continuous line) and albino (dotted line) rabbits. **b** a-wave mean amplitude and standard deviation for albino and pigmented rabbits. **c** b-wave mean amplitude and standard deviation for albino and pigmented rabbits; vertical bars = SD; vertical bars = SD; *p < 0.0001; **p < 0.00001

Photopic ERG

pigmented (English Butterfly)
albino (New Zealand)
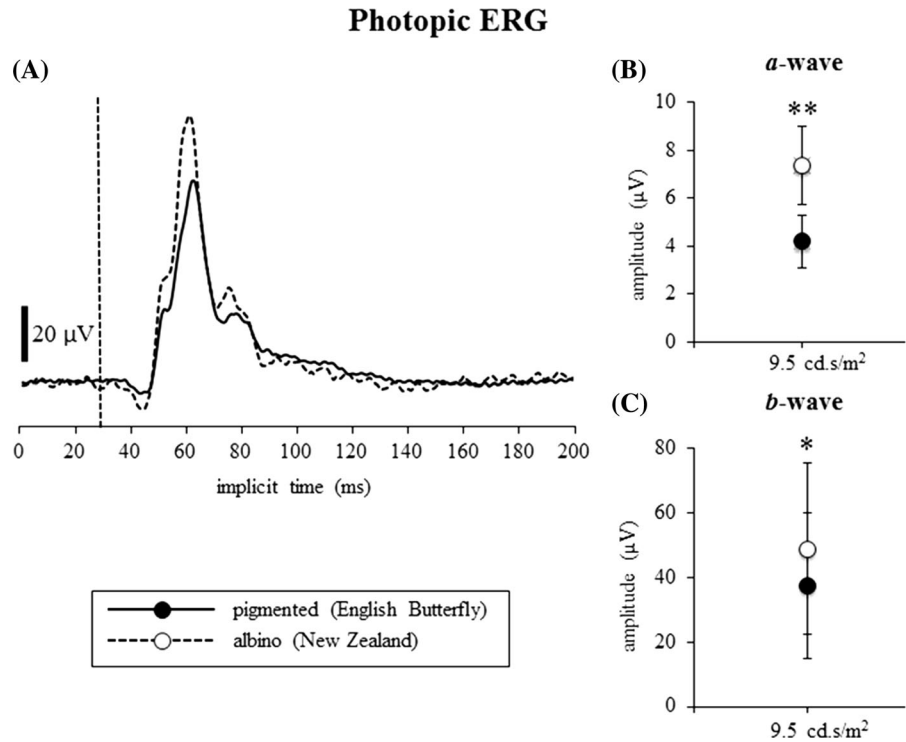
Table 2 Photopic ERG averages, SD and *p* value of a- and b-waves amplitude and implicit time measured after 2 and 10 min of light adaptation for albino group

Albino	2 min	10 min	*p* value
a-wave			
Implicit time (ms)	13.3 (0.7)	13.9 (1.2)	0.14
Amplitude (mV)	11.5 (2.7)	8.2 (1.9)	0.09
b-wave			
Implicit time (ms)	30.8 (0.7)	33.3 (3.5)	0.13
Amplitude (mV)	81.36 (12)	102.1 (24)	0.12

Table 3 Photopic ERG averages and SD of a- and b-waves amplitude and implicit time measured after 2 and 10 min of light adaptation for pigmented rabbits

Pigmented	2 min	10 min	*p* value
a-wave			
Implicit time (ms)	15.2 (0.8)	15.3 (0.7)	1
Amplitude (mV)	12.0 (3.0)	12.9 (1.9)	0.49
b-wave			
Implicit time (ms)	33.9 (3.9)	33.8 (3.8)	0.66
Amplitude (mV)	55.8 (23.3)	53.2 (16.3)	0.68

associated with the underdeveloped central retina caused by the lack of ocular melanin that regulates the maturation of the neural retina. This phenomenon was described comparing photoreceptor topography between albino and pigmented ferrets showing a decrease in the number of photoreceptors [36]. With similar results, Jeffery and colleagues compared photoreceptor distribution in albino and pigmented mice and showed that the number of rods was reduced by approximately 30% in albino animals [37].

As some species present larger ERG responses for albinos and others for pigmented, inferences about the role of the ocular melanin and its effects on the ERG are still obscure and we can conclude that the greater amount of light that reaches the photoreceptors in albino rabbits, due to the lack of melanin in the RPE, may not be the sole factor explaining the larger ERGs, since this does not hold for some albino mice and rats, whose ERGs are smaller than in pigmented individuals.

These different electrophysiological characteristics found in different species emphasize how critical is the choice of an animal model for pharmacological studies, once the drug–melanin binding may interfere

Fig. 6 Representative photopic flicker responses for pigmented (continuous line) and albino (dotted line) rabbits at 12, 18, 24 and 30 Hz
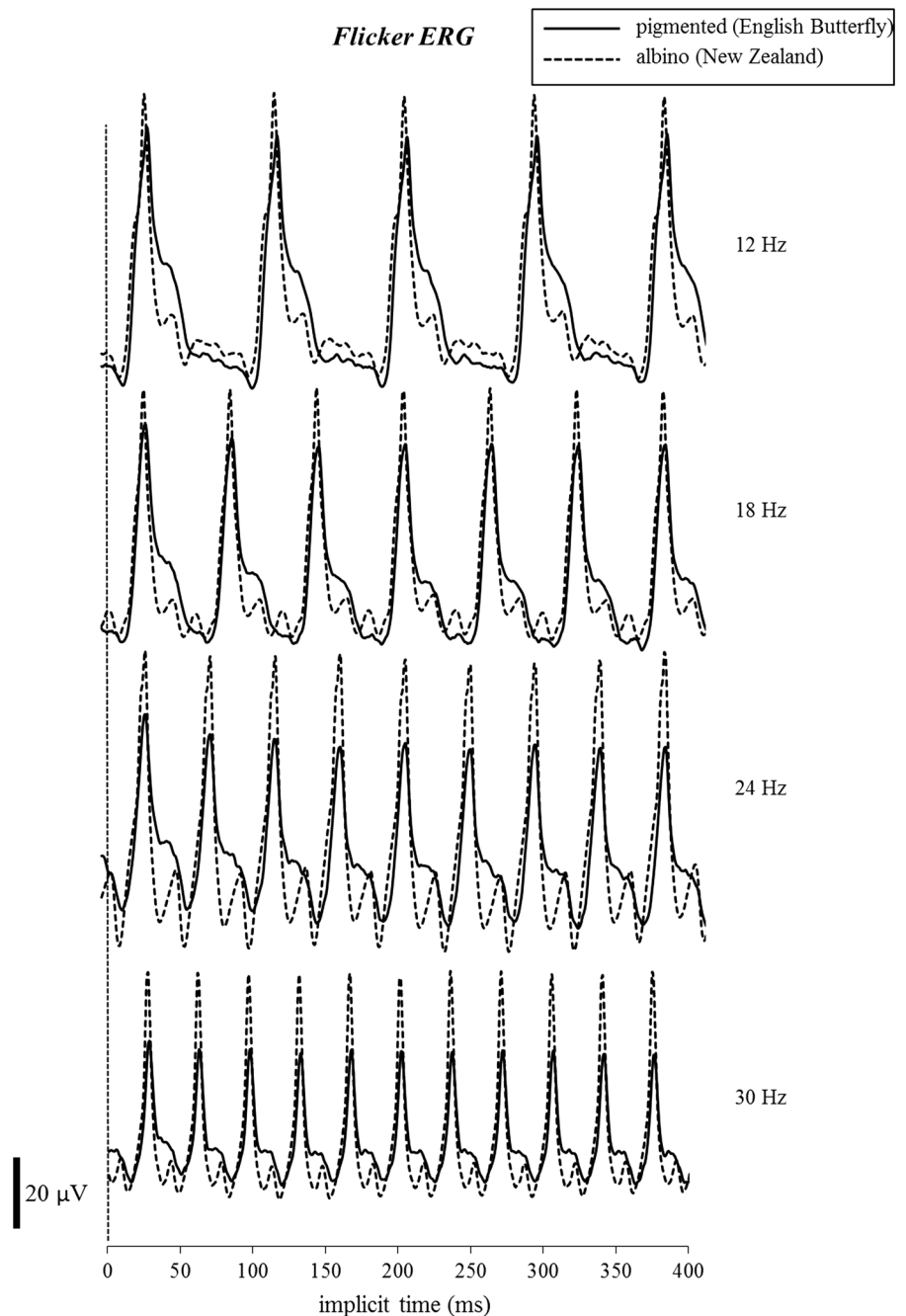
in ocular drug toxicity results. In pigmented animals, drugs that are mainly basic and lipophilic are attracted and retained by the RPE. This retention in the RPE lengthens the exposure of the tissues to the drug, increasing the risk of damage. The RPE may thus be responsible for altering the toxicological characteristics of pigmented animals [38, 39]. Conversely, ocular pigmentation has also been shown to protect the retina from some types of drugs [40, 41, 42].

These variables indicate that the presence or absence of melanin influences the toxicological profile of the ocular drugs.
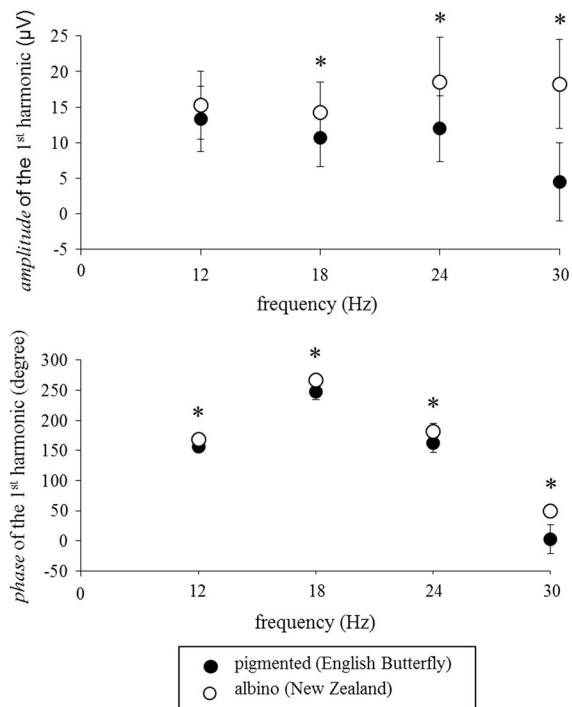
Fig. 7 Mean amplitude (above) and phase (below) of the FFT first harmonic of pigmented and albino rabbits at four different frequencies: 12, 18, 24 and 30 Hz, vertical bars = SD, *$p < 0.0001$

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All applicable international, national and/or institutional guidelines for the care and use of animals were followed. All experimental methods and animal care procedures adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and were approved by the Committee for Ethics in Animal Research, Instituto de Psicologia, Universidade de São Paulo.

Informed consent This article does not contain any studies with humans performed by any of the authors.

Statement of human rights This article does not contain any studies with humans performed by any of the authors.

Statement on the welfare of animals All procedures in this studies involving animals were performed in accordance with national and institutional guidelines for the care and use of animals. The procedures were approved in accordance with national law by the ethical standards of the institution (CEPA 001.2013).

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