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Scotopic threshold responses to infrared irradiation in cats

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Abstract

Infrared (IR) irradiation is frequently used in ophthalmological diagnosis and treatment. It has been used to selectively stimulate photodiode-based retinal prostheses to prove their function. Data concerning the natural IR-sensitivity of the retina are contradictory. In our experiments in dark-adapted cats an IR-laser (826 nm) and IR emitting diodes (875 nm) elicited clear scotopic threshold responses. Comparison of the two lasers (IR and a visible laser at 670 nm) using Lambs template and our experimental data revealed very similar differences in retinal sensitivity (4.28 and 3.94 $\pm$ 0.29 log units, respectively). The fact that the cat retina is sensitive to IR-irradiation under certain conditions has important implications in interpreting the results from retinal prostheses and rewards further attention in its use in many ophthalmological applications.

Keywords: Cat retina; Electroretinogram; Infrared; Scotopic threshold response; Sensitivity; Subretinal prosthesis

1. Introduction

In the expanding field of retinal prostheses (Chow & Chow, 1997; Chow et al., 2004; Chow, Packo, Pollack, & Schuchard, 2003; Chow & Peachey, 1998; Gekeler, Schwahn, Stett, Kohler, & Zrenner, 2001; Hesse, Schanze, Wilms, & Eger, 2000; Humayun, 2001; Humayun, Sato, Propst, & de Juan, 1995; Kohler, Hartmann, Werts, & Zrenner, 2001; Laube et al., 2003; Pardue et al., 2001b; Rizzo, Loewenstein, & Wyatt, 1999; Rizzo et al., 2001; Schanze, Wilms, Eger, Hesse, & Eckhorn, 2002; Schwahn et al., 2001a; Stett, Barth, Weiss, Haemmerle, & Zrenner, 2000, 2002; Zrenner et al., 1997) infrared (IR) irradiation has been used to selectively stimulate retinal prostheses under the assumption that silicon-based implants using photodiodes are inherently sensitive for IR-wavelengths whereas the retina is not (Chow et al., 2001, 2002; Gekeler et al., 2001; Laube et al., 2004; Pardue et al., 2001b; Peyman et al., 1998; Schwahn, Gekeler, Kohler, & Zrenner, 2001b; Zrenner, 2002). It is essential to establish a proper way of testing retinal prostheses to ascertain beyond doubt that any measured biological response is mediated by the implant and does not stem from direct stimulation of retinal cells. Since the cat is the most widely used and understood animal in respect to the visual system many groups have performed studies in these animals (Chow et al., 2001; Hesse et al., 2000; Pardue et al., 2001b; Sachs & Gabel, 2004; Schwahn et al., 2001b).

IR-irradiation is also widely used in diagnosis and treatment of ocular disease, e.g., IR emitting diodes (IREDs) or lasers are used in optical coherence tomography (OCT), retinal photocoagulation, indocyanine green angiography, transpupillary thermotherapy, in many common autorefractors, and in continuous fundus visualization during stimulation in focal macular electroretinography (Miyake & Awaya, 1984) and in the scanning laser ophthalmoscope (Seeliger & Narfstrom, 2000; Seeliger, Narfstrom, Reinhard, Zrenner, & Sutter, 2000).

There has been, however, considerable debate about the natural sensitivity of the mammalian retina to

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IR-irradiation (Chan, Freeman, & Cleland, 1992; Guenther & Zrenner, 1993; He & Loop, 1992; Jacobs & Neitz, 1986; Nelson, 1985; Ringo, Wolbarsht, Wagner, Crocker, & Amthor, 1977). Pardue et al. (2001a) have published a report which intends to demonstrate that the cat retina is sensitive to IR-irradiation by using IREDs. IREDs emit light in a wider wavelength range which is described by their half-bandwidth and therefore could stimulate the retina with the visible part of their irradiation spectrum. This prompted us to investigate in more detail the cat retina's sensitivity to IR-irradiation by using monochromatic lasers. Clear responses to IR-irradiation near the absolute threshold of vision will be shown and discussed in relation to previous reports.

2. Materials and methods

2.1. Animals

Three healthy adult cats were included in the study. After intramuscular anesthesia with ketamine (15 mg/kg) and xylazine (1 mg/kg) the animals were placed in a modified stereotactic apparatus in front of the stimulation device with dilated pupils. Experiments were either performed in the dark-adapted state after keeping the animals in complete darkness for 60 min or in the light-adapted state with a diffuse background from room illumination (approximately 2000 lx; measured with an IL 1700, international light, Newburyport, Massachussetts, USA). All experiments adhered to the ARVO statement for the Use of Animals in Ophthalmic and Vision Research and the local commission for animal welfare.

2.2. Irradiation sources

Three different irradiation sources were used in the study:

1. An IR-laser, peak wavelength $\lambda = 826.4$ nm (made by Power Technology, Mabelvale, Arizona, USA, distributed by Laser 2000 GmbH, Wessling, Germany; model number PPMT125(830-150)D2G3). Maximum Corneal irradiation was 23.0 mW (measured with a LaserMate-Q by Coherent, Santa Clara, California, USA).
2. Infrared emitting diodes, peak wavelength $\lambda_{peak} = 875$ nm, half bandwidth $\lambda_{half} = 37$ nm (HSDL-4230 by Agilent Technologies, Böblingen, Germany). Four diodes were glued together and electrically connected in series. The IREDs were positioned directly in front of the eye for stimulation and driven by 10 V. IREDs produced a corneal irradiation of 0.01 mW.
3. A red, visible laser, peak wavelength $\lambda = 670$ nm (by Laser 2000, Wessling, Germany; model number ILE-LDA 1010-1mW-M). Maximum corneal irradiation was 0.2 mW.

The spectral distribution of the irradiation sources and the sensitivity of the cat's photoreceptor pigments are given in Fig. 1. Irradiation sources were used in the above order first in the dark-adapted state and after 10 min of light-adaptation in the light-adapted state.

2.3. Stimulating setup

The IR-laser and the visible laser were mounted on the side of the chassis of a fundus camera for human use (Olympus, Hamburg, Germany; model type GRC-W) and were aligned by using a band-pass filter/mirror (Melles Griot, Bensheim, Germany). Therefore, the visible laser could also be used as a pilot laser for the IR laser. By changeable mirrors the beam could be adjusted to fall completely into the open pupil of the animal. The irradiation fell through a slightly diffusing corneal contact lens electrode. The diameter of the illuminating circle on the back of the eye was tested with both laser types and the IREDs in an artificial eye (for the IR sources an IR-sensitive digital video camera was used). It was found to be larger than 3 cm and covering the entire posterior pole. The intensity of the lasers was modified by mounting different neutral density filters (Melles Griot, Bensheim, Germany) or a combination thereof into the optical path. In a first preliminary series D 5.7, D 4.7, D 4, D 3, D 1.7, D 1.3, D 1, D 0.7, D 0.3, and no filter were used starting from the higher

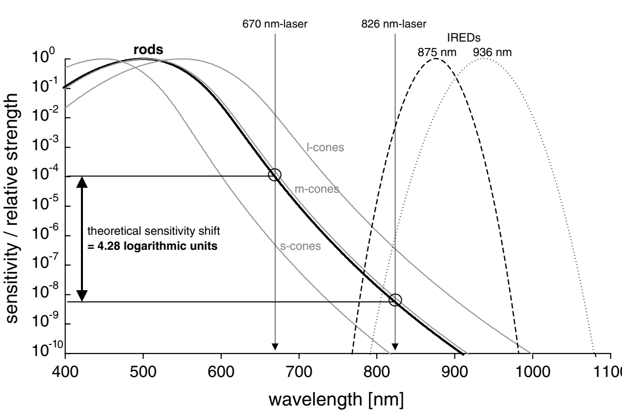

Fig. 1. Spectral sensitivity of the cat's photoreceptor pigments (Guenther & Zrenner, 1993) in relation to the spectral distribution of the infrared emitting diodes (IREDs) and the two lasers used in this study. The sensitivity shift between the two laser sources used in this study has been calculated for the rod photoreceptor pigments (any response to IR-irradiation was abolished in the light-adapted state) and yields 4.28 logarithmic units. While laser irradiation is monochromatic the spectrum of IREDs [in this and a previous study (Pardue et al., 2001a)] is broad and overlaps in a wide range with all photoreceptor pigments.

densities. The experimental series, however, was started only about two steps below the threshold found in the preliminary series. The corneal irradiation was: 0.0023 mW (D 4 filter), 0.023 mW (D 3), 0.459 mW (D 1.7), 2.3 mW (D 1), 4.59 mW (D 0.7), 11.53 mW (D 0.3), and 23 mW (no filter) for the IR laser. For the visible laser it was 0.0002 mW (D3 filter), 0.002 mW (D 2), 0.004 mW (D 1.7), 0.02 mW (D 1), 0.04 mW (D 0.7), 0.1 mW (D 0.3), and 0.2 mW (no filter). The contact lens electrode did not filter out radiation in significant amounts (less than 5%). Irradiation sources were thus used as a variation of a Maxwellian viewing system and all energy on the cornea fell completely through the pupil into the eye. Lasers and IREDs were triggered by a function generator (MCS STG 1008 by Multichannel Sytems, Reutlingen, Germany). Stimulating frequency was 0.87 Hz (inter-stimulus interval = 1540 ms; to reduce noise from 50 Hz-ground after averaging) with a pulse length of 4 ms for the lasers (based on the ISCEV standard; www.iscev.org) and 0.85 ms for the IREDs.

2.4. Electrophysiological recordings

Surface electroretinograms (ERGs) were recorded with a gold-ring contact lens electrode (ERGJet, Universo, La Chaux-de-Fonds, Switzerland) on the cornea as active electrode. One subcutaneously placed needle near the lateral canthus served as negative electrode, one needle in the midline on the scull as reference electrode.

For all recordings an ESPION Console (Diagnosys LLC, Littleton, MA, USA) was used. Data were stored on the hard disk for offline analysis. Bandpass filter settings were 0.03 Hz as low and 300 Hz as high cut-off frequency.

3. Results

3.1. Dark-adapted state

The IR-laser elicited a clearly discernible negative response starting at a corneal irradiation of 0.46 mW. Fig. 2 shows the results from one representative cat. A trough of increasing amplitude was observed starting at around 50 ms and returning to baseline at around 400 ms. Starting at 0.46 mW amplitude increased with increasing stimulus intensity from 4 ± 1, to 9 ± 4, 11 ± 7, 13 ± 9, and 18 ± 10 μV, respectively (values are given as average of three cats ± standard deviation). Implicit time decreased from 173 ± 6 to 149 ± 20, 125 ± 3, 129 ± 8, and 124 ± 7 ms. At 23 mW a small elevation appeared at approximately 50 ms.

The IREDs also elicited a clearly discernible negative response. The course of the trough followed the one described for the IR-laser with an implicit time of 140 ± 26 ms and an amplitude of 15 ± 5 μV (Fig. 2).

The visible laser elicited a clearly discernible negative response starting at 0.0002 mW with a trough of 9 ± 4 μV at 147 ± 15 ms (values are given as average from three cats ± standard deviation). Fig. 3 shows the results of one representative cat. At 0.004 mW the trough measured 20 ± 13 μV at 139 ± 11 ms. The trough thus first increased in amplitude and then decreased with all consecutive steps. At 0.02 mW two distinct positive components started to form on top of the trough at around 40 ms and at around 85 ms. Both peaks steadily increased in amplitude with increasing stimulus intensity to reach a maximum of 13 ± 4 and 76 ± 27 μV, respectively. Implicit time of the trough was around 120 ms but its amplitude cannot be

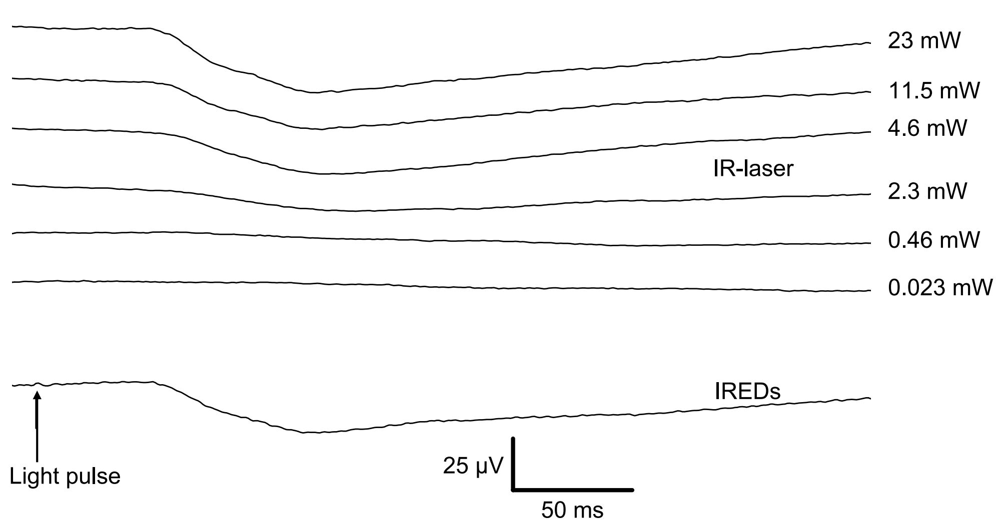

Fig. 2. Corneal electroretinograms in response to IR-laser (826 nm) and IRED (peak wavelength 875 nm) stimulation after 60 min dark-adaptation in one representative cat. A clear response can be observed from the IR-laser starting at a corneal irradiation of 2.3 mW with a trough at around 50 ms. The amplitude of the trough increased with further increasing irradiation levels. A similar response was found following illumination with IREDs. The responses are scotopic threshold responses known from visible light.

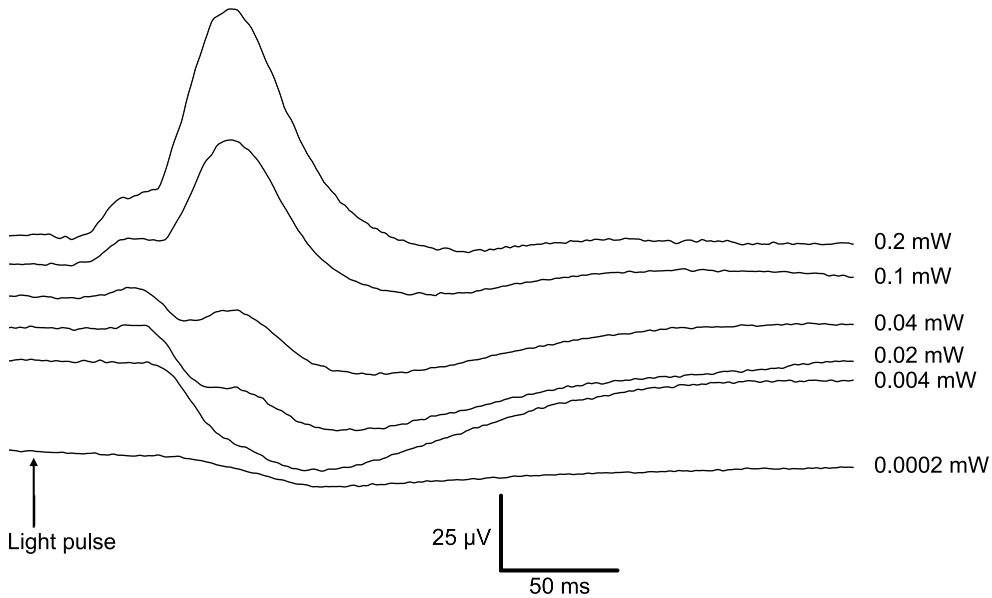

Fig. 3. Corneal electroretinograms in response to a visible laser (670 nm) after 60 min dark-adaptation in one representative cat. The visible laser elicited a scotopic threshold response (STR) with the typical trough starting at a corneal irradiation level of 0.0002 mW. With increasing amplitude the trough of the STR was overlaid by two positive peaks which are cone and rod b-waves; the first appearing at around 40 ms, the latter at around 90 ms.

measured meaningfully at higher stimulus intensity due to the overlying strong positive components.

To compare the sensitivity of the cat retina for the IR laser and the visible laser intensity–response functions were calculated in all three cats (Fig. 4). The sensitivity shift has been calculated at intensity levels of 0.15, 0.30, and 0.45. The comparison intensities were chosen in such a way that they would lie within the range of expected linearity of the intensity–response functions and within the range for which data from all three cats were available (eight out of nine values could be calculated). The values are summarized in Table 1. The average sensitivity shift for all intensity levels of all three cats was 3.94 ± 0.29 logarithmic units.

3.2. Light-adapted state

Neither the IR-laser nor the IREDs elicited discernible responses in the light-adapted state at their respective highest stimulation strengths (Fig. 5).

The visible laser elicited a clearly discernible response starting at a corneal irradiation of 0.2 mW with a positive peak of 5 ± 2 μV at 23 ms followed by a trough at around 100 ms; although a response can be anticipated at lower irradiation levels, possibly starting at 0.1 mW (Fig. 5).

4. Discussion

The ERG response to stimulation from the IR-laser in the dark-adapted condition with a trough appearing near the threshold of vision and an increasing amplitude with increasing stimulus intensity (Fig. 2) resembles the response which has been defined by many investigators as the scotopic threshold response (STR) (Finkelstein, Gouras, & Hoff, 1968; Frishman, Sieving, & Steinberg, 1988; Sieving, Frishman, & Steinberg, 1986b; Sieving & Nino, 1988). They have described the response as occurring near the absolute threshold of vision as a negative trough with a latency of roughly 50 ms and an implicit time of 120 ms. Originally, STRs were recorded in cats in response to long stimuli of 250 ms (Sieving, Frishman, & Steinberg, 1986a, 1986b). However, it is known from humans that it is possible to record STRs with 10 μs-flashes (Sieving & Nino, 1988), much shorter than the 4 ms used in our study. The similar wave-form and time course in the response to the IREDs (Fig. 2) also represents a STR.

The visible laser elicited a more complex waveform which also commenced near the absolute threshold of vision as a STR (Fig. 3). It has been described previously by e.g., Finkelstein et al. (1968) that the amplitude of the STR first rises with increasing stimulus intensity to later disappear or give rise to an overlying b-wave. In our study (Fig. 3), starting at 0.02 mW, the development of two positive waves appearing on top of the trough was observed. From its implicit time the first positive peak appearing at around 40 ms represents the cone b-wave, whereas the second one at around 85 ms represents the rod-b-wave. It is known that under certain irradiation conditions it is possible to record b-waves of rods and cones simultaneously, especially for light near the red end of the spectrum (Kawasaki, Tsuchida, & Jacobson, 1971; Motokawa & Mita, 1942).

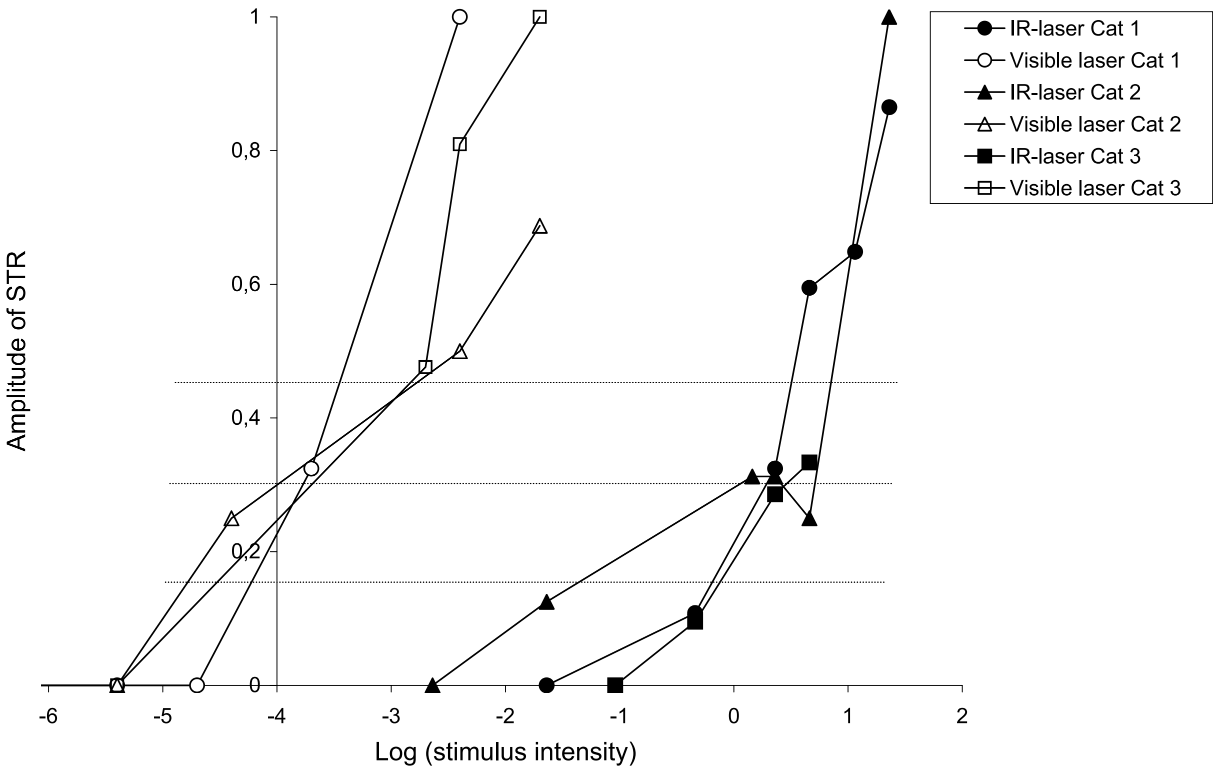

Fig. 4. Intensity–response functions of the IR-laser and the visible laser of all three cats in the dark-adapted state (logarithmic representation). Data were normalized to the maximum response of each individual cat. The shift in sensitivity between the two laser sources has been calculated individually at three levels: 0.15, 0.30, and 0.45 (fine dashed lines) in the range of expected linearity of the intensity–response functions. The average difference of 3.94 ± 0.29 is in good accordance with the expected, theoretical value of 4.28 of Lamb's template.

Table 1
Sensitivity shifts from the visible to the IR laser in three individual cats

Normalized amplitude	Shift from visible laser to IR-laser in log units		
	Cat1	Cat2	Cat3
0.15	3.40	4.05	4.40
0.30	4.05	3.93	4.10
0.45	3.60	4.00	n/a

Average of all values ± SD: 3.94 ± 0.29. Amplitudes of the scotopic threshold response (STR) were normalized to the maximum amplitude in each cat and shifts were calculated from interpolated original points at three levels (0.15, 0.30, and 0.45) within the range of expected linearity.

It is concluded that all responses to the IR-laser, the IREDs, and the visible laser in the dark-adapted state represent true ERGs and do not reflect direct, inadequate excitation of retinal neurons by heat (no matter which cell type) because, first any response disappeared in the light-adapted state, and second the implicit time is too long to reflect direct excitation by heat. Other pigments and photosensitive cells could be expected to be stimulated by the IR-irradiation, e.g., melanopsin which is known to be present in retinal ganglion cells to modulate circadian rhythms and provide non-rod, non-cone photoreception (Foster et al., 2003; Sekaran, Foster, Lucas, & Hankins, 2003; Sollars et al., 2003). Melanopsin, however, absorbs maximally near the blue end of the spectrum (Newman, Walker, Brown, Cronin, & Robinson, 2003) and is therefore unlikely to produce a STR at 826 nm. In addition, it has not been possible to demonstrate electrophysiological results from melanopsin containing cells.

In the light-adapted state only the visible laser elicited a clear response at 0.2 mW with a small b-wave (Fig. 5). At 0.1 mW the typical trough of a b-wave can only be anticipated. In contrast, neither the IR-laser nor the IREDs elicited a discernible response at their respective highest stimulation strengths. This finding is consistent with the findings of Pardue et al., 2001a who have reported that any response to IREDs was abolished by dim light. The ERG response which could be recorded to the IR-laser and the IREDs in the dark-adapted state stems from the rod system and is accordingly suppressed in the light-adapted state because of the shift in sensitivity in the light-adapted retina.

Using the template of Lamb Lamb (1995) the sensitivity for the cat's rods (maximum at 501 nm) was calculated to be 9.41×10^{-5} at 670 nm (visible laser) and 4.86×10^{-9} at 826 nm (IR laser). The theoretical difference therefore in sensitivity between the two light sources is approximately 4.28 log units. The average sensitivity shift in the cats of this study was

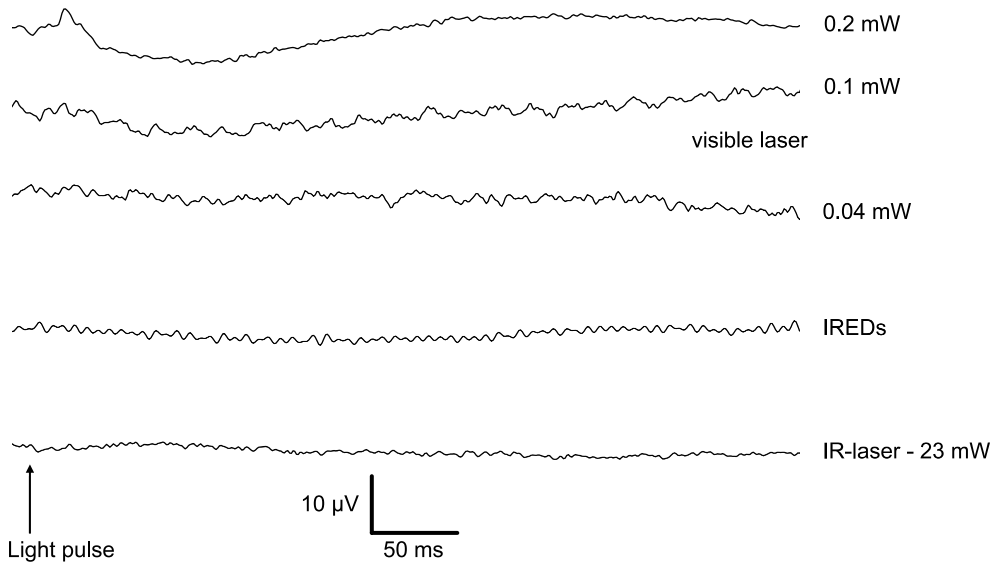

Fig. 5. Corneal electroretinograms in response to IREDs, IR-laser, and visible laser in the light-adapted state. Only the visible laser elicited a discernible response starting at corneal irradiation of 0.1 mW with a typical cone b-wave. The IR-laser and the IREDs did not elicit any discernible response in the light-adapted state.

3.94 ± 0.29 (calculated from Fig. 4 in Table 1) and corresponds well to the fit of Lamb Lamb (1995). While it is generally assumed that the STR stems from a rod response, it has been argued that cones might be involved (Sieving & Nino, 1988). The values of the sensitivity shift for the S-, M-, and L-cones calculates to be 3.86, 4.32, 4.60 logarithmic units, respectively, and also compares well to the value found in our study. The accordance of our value with the theoretical value adds experimental, electrophysiological proof for Lamb's template in the IR region. Accordingly, irradiation in the deep IR region produced not only undefined retinal response but well-described STRs of quasi identical form as from visible light, but also—when adjusted to the theoretical difference in sensitivity (approximately 4 logarithmic units)—of similar amplitude. This might suggest that also other features of the ERG such as b-wave will be measurable from IR-laser irradiation with higher irradiation power. However, intensity of the IR-laser in our case was limited to a corneal irradiation of 23 mW.

For retinal prostheses it is mandatory to prove their function, first in laboratory animals and also later in humans. In light-sensitive prostheses based on silicon, or more specifically in subretinal implants with photodiodes, use of IR-irradiation has been a way of selectively stimulating the implants which are inherently sensitive also in the IR-range while the retina has been assumed to be insensitive to the wavelengths used (Chow et al., 2002; Zrenner et al., 1999). Pardue et al. (2001a) have reported cortical responses to retinal irradiation from IREDs in cats. It remains however unclear if the responses were indeed elicited by IR-irradiation or from shorter wavelengths within the emission spectrum of these high power IREDs. In our study, we have found a clear retinal response to IR-laser irradiation proving the cat retina's sensitivity to this wavelength of 826 nm. Because laser light is monochromatic there is no possible confusion with responses from other wavelengths as with IREDs. Although careful interpretation is required because many differences exist between our study and the previous study concerning the recording site (retinal vs. cortical), the stimulus duration (4 vs. 200 ms), and the irradiation source (IR-laser vs. IREDs) our result is in good accordance with the previous findings in that responses to IR-irradiation were only found in the dark-adapted state while they disappeared in the light-adapted state. It confirms the previous study by demonstrating retinal sensitivity to irradiation of IREDs.

In conclusion, we have shown that there is native sensitivity of the cat retina to IR-irradiation. To our knowledge this is the first description of an unequivocal response to IR irradiation in the mammalian retina. From Lamb's template (Lamb, 1995) minute sensitivity even in this wavelength region was to be expected and our responses with features of a standard ERG are evidence that the response stems from the photoreceptor system. These findings justify great care in the interpretation of results obtained from stimulation of light-sensitive retinal implants with IR-irradiation. However, any retinal response from IR-irradiation was abolished in the light-adapted state even in experimental animals with healthy retinae and with very high stimulus intensities. It seems therefore safe to propose that selective stimulation of photodiode-based prosthesis needs to be performed in the light-adapted state.

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