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Inner Retinal Function in Hereditary Retinal Dystrophies

Key Words

Retinal dystrophy
Pattern electroretinogram
On-/off-electroretinogram
Inner retina
Macular degeneration

Abstract

Hereditary retinal dystrophies are most often disorders of photoreceptors and/or the retinal pigment epithelium. Structures secondary to the photoreceptor layer such as bipolar, horizontal, amacrine and ganglion cells are secondarily involved. In later stages of the disease a mild to moderate loss of inner retina occurs, but the second and third neurons remain surprisingly viable even in late and severe stages of retinal dystrophies. The function of the inner retina in patients suffering from hereditary retinal dystrophies is not easy to determine because it depends on the input of photoreceptors. The electroretinogram (ERG) offers several possibilities in this respect: b-wave, off-response (off-ERG), oscillatory potentials, scotopic threshold response of the flash ERG and the pattern ERG (PERG). We looked at two ERG tests: the PERG and the off-ERG. The PERG is an indicator of ganglion cell function. Its amplitude is related to the photoreceptor input determined by the flash ERG and visual field testing. But in cases of an undetectable flash ERG response the PERG can be recorded in some patients, but not in others. This may be an indication of a different effect on inner retinal function in different groups of patients. On- and off-responses are related to the function of depolarizing and hyperpolarizing bipolar cells. Evaluation of 301 patients with various retinal dystrophies revealed that most hereditary disorders primarily affect the photoreceptors or the pigment epithelium. In some patients, alterations of the on- and off-response amplitudes or implicit times were indicative of inner retinal disorders and different pathophysiologic mechanisms. However, interpretation has to be made carefully, as on- and off-responses may be influenced by dysfunction of photoreceptor synapses to bipolar cells, bipolar cells, Müller cells and intercellular matrix.

Introduction

The majority of hereditary retinal dystrophies originate within the outer retinal layers. Clinical evaluations in retinitis pigmentosa (RP), cone, cone/rod dystrophies and hereditary macular dystrophies as well as genetic studies indicate that in many of those diseases the underlying pathogenetic

Abbreviations used in this paper:

ERG = Electroretinogram; ISCEV = International Society for Clinical Electrophysiology of Vision; LED = light-emitting diode; MAR = melanoma-associated retinopathy; PERG = pattern electroretinogram; RP = retinitis pigmentosa; STR = scotopic threshold response.

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defect is located in the photoreceptor layer or in the pigment epithelium [Bird, 1992; Bird, 1995; Zrenner et al., 1995; Moore and Evans, 1996; Gu et al., 1997]. Accordingly, shortening, disorganization and finally loss of photoreceptors and degeneration of pigment epithelium cells can be observed by light and electron microscopy. A secondary degeneration of the middle and inner retinal layers could be caused by a transsynaptic degeneration or by toxic products associated with the death of outer retinal structures.

Evaluation of inner retinal layers in retinal dystrophies was triggered by reports of disorders associated with a predominant reduction of the electroretinogram (ERG) b-wave (so-called 'negative ERG') indicating an inner retinal dysfunction. A negative ERG has been described in stationary and progressive hereditary retinal disorders as well as acquired retinal dysfunctions. Hereditary disorders were congenital stationary night blindness [Miyake et al., 1986, 1987] and the following progressive disorders: x-linked retinoschisis [Peachey et al., 1987], subtypes of cone dystrophies [Kellner and Foerster, 1993], RP [Cideciyan and Jacobson, 1993] and macular dystrophy [Miyake et al., 1989; Kato and Watanabe, 1990], Duchenne muscular dystrophy [Pillers et al., 1993], and Müller cell sheen dystrophy [Gass, 1997; Kellner et al., 1998]. An acquired retinal dysfunction with negative ERG is melanoma-associated retinopathy [Alexander et al., 1992; Kellner et al., 1994]. These reports indicate that at least in some retinal dystrophies inner retinal neuronal or glial cells are primarily involved in the disease process.

In addition, middle and inner retinal layers in hereditary retinal dystrophies have gained more interest because some of the new potential therapeutic concepts such as transplantation of photoreceptors or pigment epithelium cells and visual prosthesis require functional second and third order retinal neurons. Morphological studies are based on the availability of post mortem eye donors and are hampered by the fact that mostly older individuals are investigated. In spite of this problem, there are some reports in the literature.

In early stages of autosomal dominant RP only disorganization and degeneration of rod and cone photoreceptors are present while the pigment epithelium layer and the inner retina are unaffected [Flannery et al., 1989]. Santos and coworkers [1997] demonstrated that even in severe forms of RP a large percentage of inner retinal neurons remains histologically intact in spite of severe photoreceptor loss. Nevertheless, there are many indications for an effect on the morphology and function of inner retinal layers. Li and coworkers [1995] reported that in RP the typical bone

spicule pigmentation located in the inner retina consists of cells from the retinal pigment epithelium. Adjacent to these cells they found atypical Müller cell processes and fenestrated vascular endothelial cells resembling the choriocapillaris. The vascular lumina were attenuated. On the functional level, Hood and Birch [1996] found that the delay in the ERG 30-Hz flicker response typical for RP might be caused by a combination of a sensitivity change at the receptor level and a delay in the response of the inner retina. Surprisingly, using flicker focal ERG, Falsini and coworkers [1994] found an increase of the fundamental-second harmonic ratio in RP patients, the second harmonic representing inner retinal function. This result suggests that macular dysfunction in RP patients is not only due to receptor but also postreceptor dysfunction.

The objective evaluation of middle and inner retinal function is hampered by the fact that electrophysiological responses of inner retinal neurons depend on the function of the photoreceptors. If there is no rod and cone function left, one cannot expect any signal from e.g. bipolar or ganglion cells. Fortunately, in many forms of hereditary retinal dystrophies, there is a remaining function of rods and cones until late stages of the disease. If this is the case, inner retinal potentials may be obtainable. Psychophysical tests, like color vision and contrast sensitivity, may also be indicative of inner retinal function but, in case of dysfunction, they do not permit the localization of the affected retinal cell layer.

In looking at inner retinal function in hereditary retinal dystrophies the following questions are of interest. Which electrophysiological test is most adequate to test inner retinal function? In which forms of retinal dystrophies (peripheral, central) can the function of the inner retina be investigated at all and how do they differ? Given a certain disease entity (e.g. RP), is there a differential effect on inner retinal function in specific genetic subgroups (e.g. rhodopsin mutations, peripherin mutations)? Is there any indication for a reduced inner retinal function even though the respective layers are morphologically well preserved? Is there a suitable test for inner retinal function to identify those patients who may profit most from potential new forms of therapy, such as photoreceptor/pigment epithelium transplantation or retinal prosthesis?

In the literature there are only a few reports about inner retinal function in hereditary retinal dystrophies, of which some have already been mentioned. In principle, the following electrophysiological tests can be used for this purpose. (1) b-wave of the full-field short-flash ERG. The main source of the corneal positive b-wave of the clinical human ERG probably is the depolarization of the bipolar cells leading to an increase in extracellular potassium and a de-

polarization of the Müller cells (glial cells) [Dowling, 1970; Newman and Odette, 1984; Ripps and Witkovsky, 1985]. While the significance of the Müller cells may have been overestimated in earlier years [Robson and Frishman, 1994], the exact role of hyperpolarizing bipolar cells and horizontal cells is still under discussion [Sieving et al., 1994]. (2) On-/off-responses. Recording an ERG using long duration flashes (30 ms and longer) the b-wave of the brief-flash ERG can be separated into an on-response and an off-response (or ERG d-wave) [Stockton and Slaughter, 1989]. The on-response reflects depolarizing bipolar cell activity at light appearance, and the off-response reflects hyperpolarizing bipolar cell activity evoked by the disappearance of light [Sieving, 1993; Sieving et al., 1994]. (3) Oscillatory potentials. The oscillatory potentials are high-frequency potentials superimposed on the ascending limb of the ERG b-wave after stimulation by an intense light flash [Yonemura, 1962]. Although the exact site of their origin is still unknown, they are probably generated in or near the inner plexiform layer [Ogden, 1973; Wachtmeister and Dowling, 1978; Yanagida et al., 1988]. Their sensitivity for retinal ischemia supports this hypothesis [Bresnick et al., 1984; Bresnick and Palta, 1987]. Possible generators are depolarizing amacrine cells [Djamgoz, 1986]. (4) The scotopic threshold response (STR). The STR of the ERG [Sieving et al., 1986] is recorded near the psychophysical absolute threshold. It shows a negative shape but differs from the ERG a-wave. Intravitreal aspartate injections showed that the STR origin is located postsynaptically to the photoreceptors [Wakabayashi et al., 1988], probably between the inner plexiform layer and the ganglion cell layer [Frishman et al., 1988]. The STR originates solely from the rod pathway [Sieving and Nino, 1988]. (5) The pattern ERG (PERG). The PERG is basically different from the above-mentioned recordings because the stimulus is not a luminance stimulus like a flash, but a pattern, usually a checkerboard or a bar grating [Riggs et al., 1964]. Maffei and Fiorentini [1981] showed that the origin of the PERG lies proximal to the flash ERG b-wave and the current hypothesis is that ganglion cells contribute most to the PERG response.

In our own investigations we had two purposes: to look at the function of the ganglion cell layer in typical RP by correlating the PERG amplitude with other visual functions; these results were compared to patients suffering from macular dystrophy, and to look at the function of bipolar cells in retinal dystrophies by recording on- and off-responses using long duration flashes.

Table 1. Normal values of on-/off-ERG (n=68)

	Range	Median	Mean ± SD
<i>On- and off-response amplitudes, μV</i>			
Green			
On	15.0–61.9	37.0	38.2 ± 9.5
Off _{200 ms}	14.9–54.5	32.4	32.8 ± 8.9
Off _{250 ms}	9.8–58.5	31.7	33.1 ± 9.7
Red			
On	21.0–63.7	42.0	40.8 ± 9.9
Off _{200 ms}	8.3–45.5	21.2	23.6 ± 8.3
Off _{250 ms}	9.7–46.7	24.5	24.0 ± 8.2
<i>On- and off-response implicit time, ms</i>			
Green			
On	26.0–41.0	33.0	32.8 ± 3.2
Off _{200 ms}	20.0–26.0	22.0	21.9 ± 1.3
Off _{250 ms}	20.0–26.0	22.0	22.1 ± 1.2
Red			
On	29.0–42.0	33.0	33.6 ± 2.9
Off _{200 ms}	20.0–26.0	22.0	22.7 ± 1.3
Off _{250 ms}	22.0–25.0	22.0	22.9 ± 1.0

Patients and Methods

Pattern ERG

We examined 23 patients with typical symptoms of RP (rod-cone dystrophy with night blindness, visual field constriction, flash ERG reduction and bone spicule pigmentation). Four of them displayed autosomal dominant inheritance, the other patients were simplex cases, i.e. no other family members were affected. Mutation analysis was not performed. For comparison, we examined 22 heterogenous patients with macular dystrophy defined by morphological alterations of the macular area, normal peripheral visual field and normal flash ERG. In 7 patients Stargardt's disease was diagnosed. The median of age in the RP group and the macular dystrophy group was 37 and 28 years, respectively (minimum 19 and 12, maximum 65 and 67).

Our examination included the PERG, the maximal response of the flash ERG b-wave according to the standard of the International Society for Clinical Electrophysiology of Vision (ISCEV) [Marmor, 1995], central visual field radius (kinetic perimetry, Goldmann stimulus III/4) and Snellen visual acuity.

The PERG was basically performed according to the ISCEV guidelines [Marmor et al., 1996]. the checkerboard stimulus was generated by a black and white monitor (15 × 17° visual angle). The check size (1.5 × 1.24° visual angle) was bigger than proposed by the guidelines (approximately 40') to reduce the influence of media opacities. The distance between the eyes of the patient and the monitor was 1 m and the patients were optimally corrected. The pupils were not dilated and the test was performed binocularly to facilitate fixation. The mean luminance of the monitor was 85 cd · m⁻² and the contrast between white and black checks 95%. Fixation was further facilitated by a red light-emitting diode (LED) in the center of the monitor. The stimulus frequency was 15 reversals/s (7.5 Hz). To obtain the corneal potentials fiber electrodes were used. Gold cup electrodes served as reference (outer canthus) and ground (forehead). The main out-

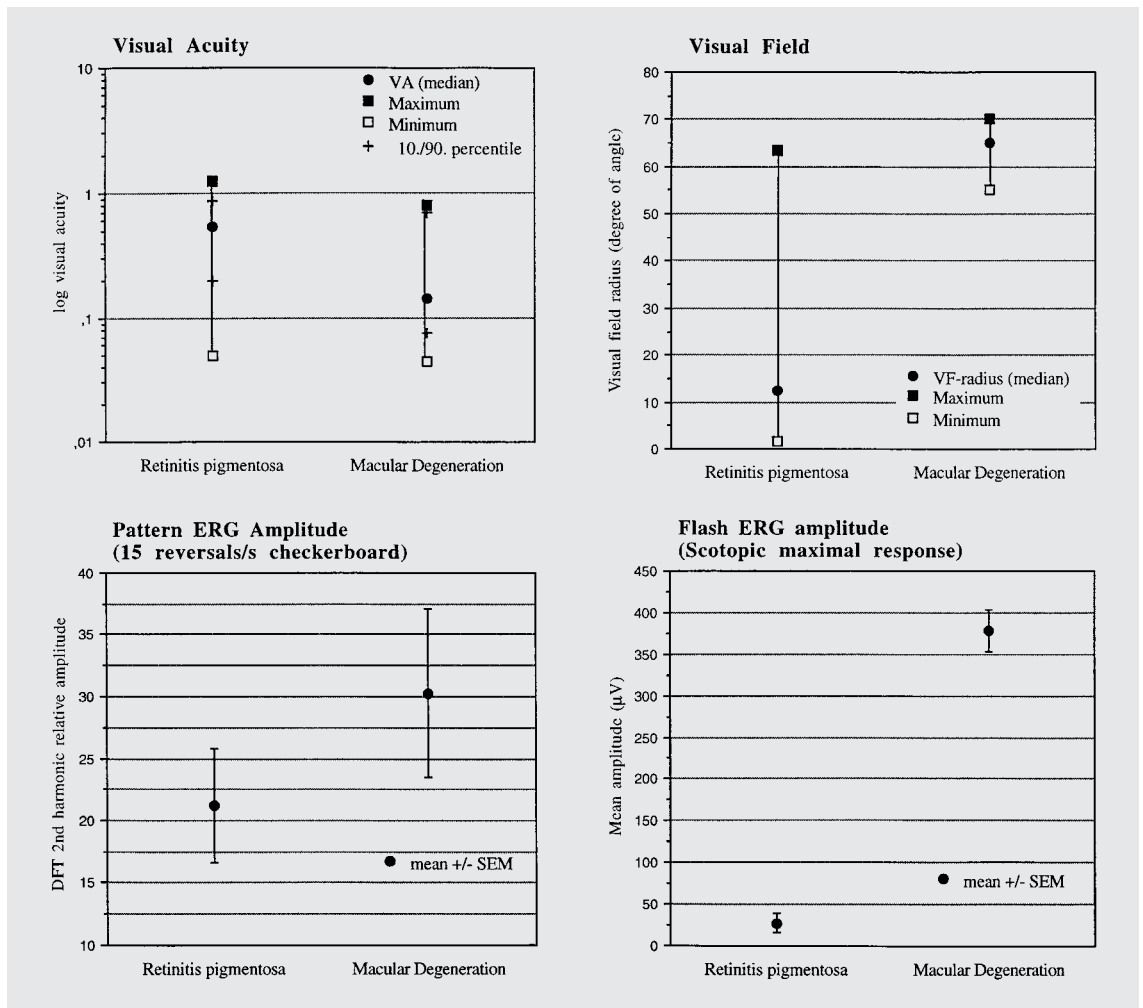


Fig. 1. Visual function data of 23 RP patients and 22 patients suffering from macular dystrophy who underwent PERG testing. DFT = Discrete Fourier transform.

come variable was the amplitude of the second harmonic determined by a Fourier transform.

The flash ERG has been recorded by the LKC UTAS-E-2000® (LKC Technology, Gaithersburg, Md., USA). The maximal intensity of the Ganzfeld stimulus was $1.7 \text{ cd} \cdot \text{s} \cdot \text{m}^{-2}$, the background illuminance for the photopic ERG was $19 \text{ cd} \cdot \text{m}^{-2}$. The scotopic ERG recorded after 30 min of dark adaptation consisted of 4 responses including the rod and maximal response according to the ISCEV standard for ERG [Marmor, 1995]. After the oscillatory potentials and a 10-min period of light adaptation the cone single and the 30-Hz flicker responses were recorded. For the description of the RP and macular degeneration patients in respect to the ERG the b-wave amplitude of the scotopic maximal response was used (fig. 1). It was measured from the trough of the preceding a-wave to the peak of the b-wave.

On-/Off-Responses

Patients (n=301) with various disorders (e.g. RP, cone dystrophies, macular dystrophy, stationary cone dysfunction, congenital sta-

tionary night blindness, x-linked retinoschisis and melanoma-associated retinopathy) were evaluated. Examination included Snellen visual acuity, color vision, Goldmann visual fields, and short-flash ERG recording according to the ISCEV standard [Marmor, 1995].

Following brief-flash ERG recording on- and off-responses were obtained with a LED stimulator (Roland Consult, Brandenburg, Germany) using either red or green LEDs ($3 \text{ cd} \cdot \text{s} \cdot \text{m}^{-2}$) and flashes of long duration (200 or 250 ms) presented on background illumination. Recordings were done after 10 min of light adaptation ($10 \text{ cd} \cdot \text{m}^{-2}$). 128 responses were averaged. Jet-corneal contact lens electrodes were used. The normal values for on- and off-responses were defined by evaluation of one eye in 68 subjects (34 ± 13 years, 18–64 years; table 1). Evaluation in subjects revealed good recordability and reproducibility of on- and off-responses. There was no difference in amplitude or latencies between both stimulus durations (200 vs. 250 ms) and no marked difference between red or green LEDs. The off-response implicit time showed small variability. The off-/on-amplitude ratio ranged between 0.41 and 1.5 (median 0.86, mean \pm SD: 0.9 ± 0.2).

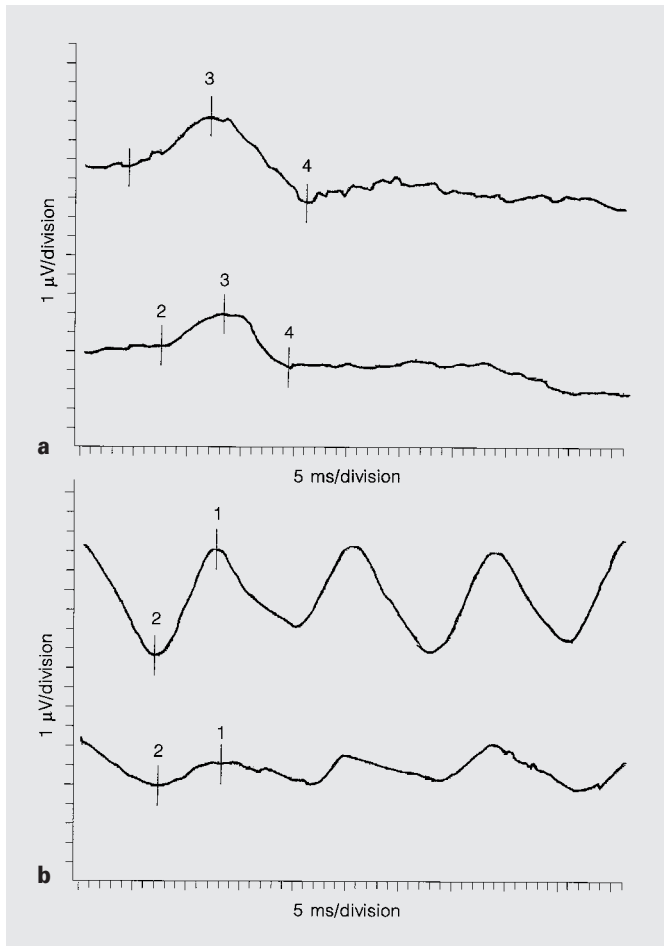


Fig. 2. **a** Transient PERG of a normal observer (top) and an RP patient (bottom). **b** Steady-state PERG of the same subjects. The RP patient had a central visual field radius of 10° and full visual acuity.

Results

Pattern ERG

Figure 1 summarizes the visual function data of RP and macular dystrophy patients. Figure 2 displays transient and steady state PERG of a normal observer and an RP patient. In both groups, RP and macular dystrophy, the mean PERG amplitude was below the lower limit of the normal range. In 7 RP patients there was no detectable PERG response. In these patients the maximal response of the flash ERG was also nearly extinguished. In contrast, 8 patients with a barely recordable flash ERG showed reproducible PERG responses. The median of visual acuity in the first group was 0.35 compared to 0.52 in the second group. The medians of the visual field radius were 7.5 and 5° in the first and

Table 2. Correlation of the PERG 15 reversals/s second harmonic amplitude and visual acuity, visual field radius, maximal scotopic b-wave amplitude and age in RP and macular dystrophy patients

RP	Macular degeneration
<i>Visual field radius</i> R=0.86	<i>Visual acuity</i> R=0.84
<i>Visual acuity</i> R=0.28	<i>Scotopic ERG maximal b-wave amplitude</i> R=0.41
<i>Scotopic ERG maximal b-wave amplitude</i> R=-0.1	<i>Visual field radius</i> R=0.34
<i>Age</i> R=-0.46	<i>Age</i> R=-0.52

The results are taken from the first step of the stepwise regression so that the R values of the 6 last categories have to be looked at partial correlation coefficients. Those correlation coefficients which are significantly different from zero are printed in bold letters [Ferguson, 1966]. The critical p value is 0.05.

second group, respectively. These differences were not significant (ANOVA, $p=0.23$).

To get an impression of correlations between the different variables we performed a stepwise regression analysis. In the RP group the first step reveals a high correlation between the PERG amplitude and the visual field radius ($R=0.86$). In contrast, in the group of macular degeneration patients the first step indicates a close relationship between the PERG amplitude and visual acuity. Looking at the partial correlations, age seems to be negatively correlated to the PERG amplitude in both patient groups. This negative correlation is independent of visual field radius and visual acuity, respectively. The relationship between PERG and visual acuity and visual field radius was estimated by the Spearman rank correlation coefficient (table 2).

On-/Off-Responses

On- and off-responses were easily recorded when photopic standard ERG responses were present. In the great majority of patients there was a similar reduction of on- and off-response amplitudes and no increase of on- and off-response implicit times. This indicates a primary defect within the outer retina or pigment epithelium without detectable secondary changes in the inner retina in most patients with retinal dystrophies. There were, however, three patterns of responses indicative of selective inner retinal effect: on-response amplitude more reduced than off-response amplitude (off-/on-amplitude ratio >2.5), off-

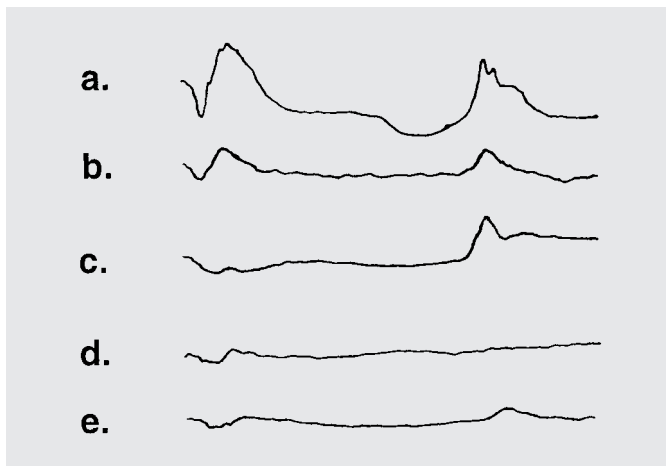


Fig. 3. On- and off-responses: a=normal recording, b=similarly reduced on- and off-response in adRP, c=on-response amplitude more reduced than off-response amplitude, d=off-response amplitude more reduced than on-response amplitude, and e=delayed off-response implicit time.

response amplitude more reduced than on-response amplitude (off-/on-amplitude ratio <0.4), and delayed off-response implicit time. Typical recordings for each pattern are shown in figure 3.

In 14 cases, the on-response amplitude was markedly reduced when the off-response amplitude was normal or borderline. As expected, this feature was seen in all patients with congenital stationary night blindness and melanoma-associated retinopathy. In addition, it was found in some patients diagnosed as RP or cone-rod dystrophy. These latter patients differed neither in morphological nor in other functional respects from other patients with RP and cone-rod dystrophy and similarly reduced on- and off-responses.

In 5 cases, the off-response amplitude was more reduced compared to the on-response amplitude. In 2 of these cases, RP and cone-rod dystrophy were indistinguishable from other patients with similarly reduced on- and off-responses. Three cases were in some way unusual: 1 female patient, followed for 16 years, had unilateral RP in her right eye, 1 female patient with RP had multiple yellow flecks and 1 male patient with a subtype of RP called 'clumped pigmentary retinal degeneration' [To et al., 1996].

In normals, the off-response implicit time had a very small interindividual variability. A moderately increased off-response implicit time (3 ms) was seen in 17 patients (5.7%). This included patients with RP, cone-rod dystrophy, congenital stationary night blindness and all 3 patients with x-linked retinoschisis. In 2 additional cases (0.7%)

implicit times were markedly prolonged (7 and 12 ms): 1 case was diagnosed as RP and the other as cone-rod dystrophy. These patients differed neither in morphological nor in other functional respects from patients with RP and cone-rod dystrophy and normal off-response implicit time.

Discussion

Pattern ERG

ERG and PERG differ in two aspects: origin and sampled retinal extent. The PERG is believed to be mainly influenced by the function of the ganglion cell layer. However, it cannot be excluded that there is a contamination of other retinal layers, in particular of the outer retina. Although the stimulus conditions were chosen to avoid any contamination of light instead of pattern it is not possible to achieve this completely. In addition to its relative specificity to the ganglion cell layer the pattern ERG is also a kind of local ERG, because only the center of the retina is stimulated by the pattern.

Analyzing the PERG in patients suffering from a peripheral retinal dystrophy such as RP showed that there was a high correlation between the visual field radius and the PERG amplitude. This was expected because the ganglion cell function depends on the receptor input which seemed to be better reflected by the visual field radius than by the scotopic ERG maximal b-wave amplitude. This might be explained by the fact that PERG and the visual field are dependent on cone function whereas the maximal b-wave amplitude of the scotopic ERG is determined by residual rod and cone function. Even more relevant may be the fact that maximal b-wave response could only be recorded in about 35% of the patients.

In patients suffering from macular dystrophy, the most important correlation was revealed between PERG and visual acuity. In addition, the scotopic ERG maximal b-wave amplitude seems to be correlated to the PERG amplitude independently of visual acuity (partial correlation coefficient of 0.41; table 2). This result may indicate that the PERG is a parameter of macular vision and that it depends on the photoreceptor input to the ganglion cell layer. In addition, patients with a better visual acuity may have better fixation abilities and fixation is a crucial factor for the performance of the PERG. In summary, it is interesting that in both patient groups, RP and macular degeneration, the PERG amplitude is in fact correlated to the crucial visual function parameter visual field and visual acuity and that it may be a valuable diagnostic adjunct in those patients

having a nonrecordable ERG (RP) or a very bad visual acuity (macular degeneration).

In RP patients with no or nearly no flash ERG response there was one group with and one without detectable PERG responses. Those without a PERG response tend to have a smaller visual field and a worse visual acuity but the differences were not significant. This may indicate that there are patients with a more severe effect on inner retinal structures and their functions. Unfortunately, we have no information about the underlying gene defects in these respective patients.

On-/Off-Responses

The results in normals showed that recording of on- and off-responses is a reproducible and reliable test. In the majority of patients with inherited retinal dystrophies on- and off-responses are reduced to a similar extent. This finding is in accordance with the expectation that in most retinal dystrophies the primary disease process originates within the pigment-epithelium-photoreceptor complex. The findings in a minority of patients, however, suggest that in some retinal dystrophies the disease process either develops within or at least predominantly affects inner retinal layers.

On- and off-responses are related to the function of depolarizing and hyperpolarizing bipolar cells. Alterations of the on- and off-response amplitudes or implicit times are indicative for inner retinal disorders and different pathophysiological mechanisms. However, the interpretation has to be done carefully, as on- and off-responses may be influenced by dysfunction of photoreceptor synapses to bipolar cells, bipolar cells, Müller cells and intercellular matrix.

Evidence that on-response abnormalities can indeed be related to on-bipolar cell dysfunction comes from an acquired retinal degeneration, melanoma-associated retinopathy (MAR) [Alexander et al., 1992]. In some patients with cutaneous melanomas a paraneoplastic effect induces a sudden onset of night blindness and mild visual loss. Functional evaluation reveals a negative brief-flash ERG and a missing or severely reduced on-response and a normal off-response. Antibodies from the serum of all examined MAR patients in vitro label a subset of on-bipolar cells [Milam et al., 1993; Kellner et al., 1994; Weinstein et al., 1994] and it is suspected, though not yet proven, that these antibodies are produced by the cutaneous melanoma.

It is therefore of interest that on-response alterations are similar in acquired night blindness in MAR and congenital stationary night blindness. In both disorders as well as in progressive retinal dystrophies with reduced on-responses a defect in the depolarizing bipolar cells can be suspected. The findings in this series suggest that, at least in some

forms of RP and cone-rod dystrophy, depolarizing bipolar cells are primarily affected in the disease process. The off-response was only in few cases more reduced than the on-response, which indicates that defects of the hyperpolarizing bipolar cells are even less frequent.

In other disorders alterations of the timing of on- and off-responses were observed. It is of interest that in this group two disorders with histologically proven defects in the Müller cells were found: x-linked retinoschisis [Condon et al., 1986] and Müller cell sheen dystrophy [Gass, 1997]. A defect within the Müller cells could induce a delayed uptake of potassium released by the bipolar cells into the intercellular space. One could suspect that other disorders with delayed implicit times could be caused by similar defects of the Müller cell or bipolar cell membrane properties.

In conclusion, the recording of on- and off-responses in a large series of various retinal dystrophies revealed a primary involvement of inner retinal layers in a minority of patients. The clinical findings of these patients were in most cases indistinguishable from other patients with similar disorders, e.g. RP or cone-rod dystrophy. The most frequent brief flash ERG sign in patients with inner retinal involvement was a negative ERG. It can therefore be recommended to record on- and off-responses in all patients with a negative ERG. In some patients, however, a negative ERG was not seen, although the on- and off-responses indicated inner retinal involvement. In patients with similarly reduced on- and off-responses inner retinal involvement cannot be excluded. Thus, a defect in inner retinal processing may be more common than suggested by these results.

Summary Conclusion

Although inherited retinal dystrophies like RP and macular dystrophy are primarily diseases of the outer retina, inner retinal layers also undergo functional and structural changes. Specific electrophysiological tests of inner retinal function in these patients are inherently difficult because this function depends on outer retina input. Consequently, in peripheral retinal dystrophy we found a high correlation between the PERG, which is an indicator of ganglion cell function, and visual field radius, representing the residual cone function in these patients. One important result was that in RP patients without any recordable flash ERG response, PERG could be recorded in some patients, but not in others. Although this could be influenced by a couple of different factors, it may indicate that inner retinal function

is differentially affected in patients suffering from peripheral retinal dystrophies.

A difference in the effect on inner retinal layers was also evident by recording on- and off-responses. At least in some patients, inner retinal layers may have been primarily involved in the disease process based on a difference in the effect on b- and d-wave amplitudes and timing. Defects in retinal proteins expressed in bipolar or Müller cells may be the cause of progressive retinal dystrophy in these cases as has been shown for proteins in photoreceptors and retinal pigment epithelium.

Although research is still being done on therapeutic approaches, such as retinal pigment epithelium or photorecep-

tor transplantation and visual prosthesis, testing for inner retinal function in patients with hereditary retinal dystrophies may be important in future to establish the individuals for whom this kind of therapy may be promising. Beside electrophysiological tests it should be emphasized that psychophysical methods not tested here such as color vision testing or contrast sensitivity may also be very important for this goal.

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