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REVIEW ARTICLE

Visual electrophysiological responses in persons with type 1 diabetes

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Summary

Persons with type 1 diabetes show electrophysiological abnormalities of the visual system which are revealed by methods such as flash electroretinogram (FERG), oscillatory potentials (OPs), pattern electroretinogram (PERG), focal electroretinogram (focal ERG), visual evoked potentials (VEP) in basal condition and after photostress. This review reports the changes in electrophysiological responses of the different structures composing the visual system observed in persons with type 1 diabetes before the development of the overt clinical retinopathy. In persons with type 1 diabetes without retinopathy (IDD), the earlier abnormal electrophysiological responses are recorded from the innermost retinal layers and postretinal visual pathways, as suggested by impaired PERGs and delayed retinocortical time (RCT). These are observed in IDD persons with a disease duration shorter than 6 months. Further electrophysiological changes are recorded from the macula (abnormal focal ERG and VEP after photostress) in IDD persons with disease duration greater than 1 year. Additional electrophysiological changes are recorded from the middle and outer retinal layers (impaired FERG and OPs) in IDD persons with a disease duration greater than 10 years. All the electrophysiological tests show a greater degree of abnormal responses in persons with type 1 diabetes when a background retinopathy is present.

Keywords electroretinogram; visual evoked potentials; type 1 diabetes; diabetic retinopathy; visual function

Introduction

Persons with type 1 diabetes may develop visual abnormalities in addition to the presence of a true clinical retinopathy. These can be revealed by psychophysical and electrophysiological tests. Psychophysical tests, such as contrast sensitivity, color vision, and recovery of cone function after dazzling, are altered in persons with type 1 diabetes with or without a clinical retinopathy [1–4]. However, these methods, related to a subjective cortical response, do not reveal which structures of the visual system selectively contribute to their impairment. Electrophysiological methods allow the dissection and evaluation of the different structures composing the visual pathway.

The function of the entire visual pathway can be objectively assessed by recording cortical potentials evoked by patterned stimuli (visual evoked potentials, VEPs) [5]. The different retinal layers can be evaluated by recording electroretinographic signals evoked by flash or patterned stimuli (flash or pattern ERG) [6–11]. Focal ERG [12,13] and VEP after photostress [14,15] test the macular region. By comparing the VEP peak implicit time and the pattern ERG (PERG) peak implicit time, it is possible to construct an index

of neural conduction in the postretinal visual pathways (retinocortical time, RT [16,17]).

This review reports the changes in electrophysiological responses of the different structures composing the visual system observed in persons with type 1 diabetes before the development of overt clinical retinopathy.

Electrophysiologic evaluation of the entire visual pathway: visual evoked potentials (VEPs)

VEPs are defined as variations of bioelectrical potentials of the occipital cortex evoked by visual stimuli [18]. They are expressions of complex neurosensorial events linked to the transduction and transmission of neural impulses along visual pathways, from the retinal photoreceptors to the occipital cortex.

If the visual stimuli are reversed in contrast at 1 or 2 Hz, VEP is characterized by a transient response, while with stimuli reversed at 8 Hz, a steady-state VEP response is obtained. The transient VEP is characterized by several waves with three peaks, that in normal subjects appear after 75, 100 and 145 ms. These peaks have negative (N75), positive (P100) and negative (N145) polarity, respectively.

In persons with type 1 diabetes with (IDDR) or without (IDD) retinopathy, VEP responses with an increased implicit time and a decreased amplitude have been observed [19–31]. Delayed implicit time, but normal amplitudes are present in IDD persons with a disease duration shorter than 6 months [29,30]. In IDD persons with a disease duration between 1 and 20 years, VEP responses show delayed implicit time and reduced amplitudes. Although a worsening trend has been observed [31], no correlation with disease duration has been found [19,22,24,26,27,29,31]. Persons with type 1 diabetes and background retinopathy not involving the macular region show a further increase in the implicit time and a decrease in the amplitude of the VEPs [31].

Although Ziegler *et al*. [28] have shown that strict metabolic control is able to improve VEP responses, many authors, including Ziegler, have not found a significant correlation between VEP parameters and HbA_{1c} and/or glycemia [19,21,22–29]. In addition, Martinelli *et al*. [23] have shown that acute hyperglycemia does not influence the neurophysiological abnormalities detected in persons with type 1 diabetes. They suggest that these abnormalities 'are due to structural involvement of the central nervous pathways and not to functional damage induced by acute short-term hyperglycemia'.

Acute hypoglycemia may influence VEP responses [32,33], while chronic hypoglycemia, as seen in insulinoma patients, does not seem to have an influence [34].

Since it is known that VEPs represent a mass bioelectrical response of cortical visual area to visual stimuli [18], abnormal VEPs observed in IDD persons indicate a general involvement of the visual system or of one of its composing structures. Examples of VEP recordings in persons with type 1 diabetes are shown in Figure 1.

Electrophysiological evaluation of the retina: electroretinogram (ERG)

ERG is the bioelectrical response of retina to visual stimuli such as flashes (flash ERG, FERG) or structured visual models constituted by gratings or checkerboards (pattern ERG, PERG). Analysis of the different sources of the FERG and PERG signals allows the correlation between electrophysiological responses and pathophysiological conditions of different retinal layers.

Maffei and Fiorentini, after sectioning the optic nerve in cats, observed a decrease in amplitude and the disappearance of the electroretinographic signal evoked by pattern stimuli, while the electroretinographic signal evoked by flash stimuli was preserved [9–11]. The electrophysiological changes were related to ganglion cell degeneration [8,11,35], and therefore the PERG was related to the bioelectric activity of the innermost retinal layers (ganglion cells and their fibers), while the FERG

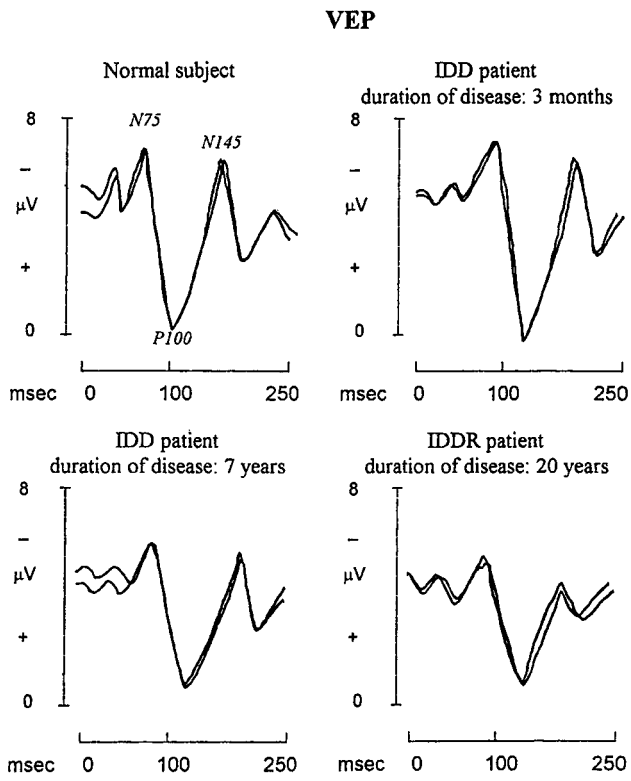

Figure 1. Examples of VEP recordings in a control subject and in persons with type 1 diabetes without retinopathy (IDD) and with background retinopathy (IDDR). In IDD with a duration of disease of 3 months, VEP recordings show delayed P100 implicit time and similar amplitudes with respect to those of control subjects. IDD with a duration of disease of 7 years presents VEP recordings with delayed implicit time and reduced amplitudes. The VEP recordings are further impaired in IDDR

signal was related to the bioelectrical activity of the outer retinal layers.

FERG

FERG represents the response of the entire retinal activity and the sensorial mechanism related to the transduction of the light stimulus to a bioelectric impulse. It is characterized by different waves which reflect the activity of different retinal structures: the a-wave reflects extracellular currents in the photoreceptor layer generated by the light absorption in the outer segments; the b-wave is considered to arise from transmembrane potential changes in the Muller and bipolar cells; the c-wave does not have a known clinical significance [36]. The oscillatory potentials (OPs) are small amplitude, high frequency waves superimposed upon the ascending portion of the b-wave [37,38]. Their origin is not well defined and is probably related to different subpopulations of amacrine cells [39].

ERG analysis consists of amplitude and implicit time measurements: the amplitude of a- and b-waves is used to assess the functional integrity of the retina; the b-wave implicit time is a marker for specific retinal disorders [7]. The OPs are considered to be the electrophysiological indicators of retinal ischemia caused by reduced circulation in the retinal blood vessels [40]. Beginning with Simonsen [41], several contributions have displayed pathologic modifications of various components of the FERG signal in persons with diabetes, and the impaired FERG responses were related to the absence or presence of retinopathy and its progression [42,43].

Uccioli *et al*. [30] have documented that IDD persons without fluorangiographic signs of retinopathy with a disease duration shorter than 6 months do not show any change in FERG and OPs, while after 10 years of disease a reduction in amplitude of the OPs appears in the absence of clinical retinopathy [31]. Coupland [42] reported that OP amplitude is significantly diminished in persons with diabetes and no photographic evidence of background retinopathy, while OPs implicit times appear to be unaffected. A similar reduction in the amplitude of OPs is reported by Brunette and Lafond [44].

Van der Torren *et al*. [38], using the Fourier analysis for measuring the OPs, have observed reduced OP amplitude in persons with early diabetic retinopathy and suggested this assessment as a reliable quantitative method to detect diabetic retinopathy at an early stage [45]. Li *et al.* [46] have also found reduced OP amplitude recorded in dark and light adaptation, in persons with background retinopathy.

Simonsen has observed that the OP amplitude predicts the progression from non-proliferative to proliferative retinopathy [47].

Bresnick and Palta [48,49] studied the timing of FERG and its relationship to the severity of retinopathy in persons with diabetes. They found that the implicit times of the first three oscillatory potentials were significantly delayed in persons with diabetes compared with controls, and that the temporal delay of the second and third OPs was correlated with the severity of retinopathy. A longitudinal follow-up study conducted by Ponte *et al*. [43] has demonstrated that diabetic persons with OPs in the normal range, that do not worsen during the observation period, do not develop retinopathy. Conversely, the OP amplitude reduction is associated with a development of retinopathy.

FERG and OPs do not correlate with the disease duration [31]. Since electrophysiological abnormalities were detected in patients with unsatisfactory glycemic control, an influence of the metabolic control has been suggested [31]. However these data are not conclusive because other authors have not tested the relationship between FERG, OPs and metabolic control [42,45,46,48]. In addition, Skrandies and Heinrich have observed that acutely induced hypoglycemia may influence the b-wave of FERG [50].

Therefore, impaired FERG and OPs indicate the presence of a dysfunction in the outer and middle retinal layers. These appear at least after 10 years of disease in persons with type 1 diabetes without clinical signs of retinopathy. FERG and OPs may display the progressive retinal involvement that occurs in persons with type 1 diabetes. Examples of Flash ERG recordings in persons with type 1 diabetes are shown in Figure 2.

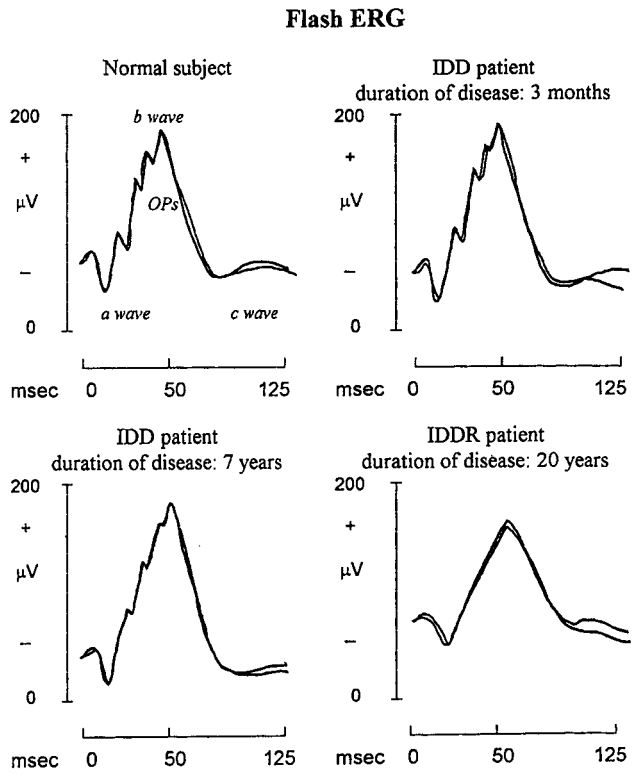

Figure 2. Examples of flash ERG recordings in a control subject and in persons with type 1 diabetes without retinopathy (IDD) and background retinopathy (IDDR). In IDD with a duration of disease of 3 months, flash ERG is similar to that of control subjects. IDD with a duration of disease of 7 years shows a reduction in the OPs amplitude while IDDR presents flash ERG with delayed a- and b-wave implicit time, reduced b-wave amplitude and absent OPs

PERG

PERG reflects the bioelectrical response of the innermost retinal layers to patterned stimuli [8–11,35]. If the visual stimulus is reversed in contrast at 1 or 2 Hz, PERG is characterized by a transient response, while with stimuli reversed at 8 Hz, a steady-state PERG response is obtained. The transient PERG is characterized by several waves with three peaks that in normal subjects appear after 35, 50 and 95 ms. These peaks have negative (N35), positive (P50) and negative (N95) polarity, respectively. The steady-state PERG response displays a major component at 16 Hz (second harmonic or 2P) and the amplitude and the phase of 2P are considered in the analysis of this response [51].

Several studies have been performed on PERG in IDD and IDDR persons. Data found in literature are controversial: some authors observed PERG in the normal range [42,52], while others recorded pathological values in IDD persons [29,53–55], also with a mean disease duration of 3.5 years [53,54]. A mild to moderate retinopathy shows pathological results of PERG parameters [37,56–58].

In our experience impaired PERG responses are present in all IDD persons with disease duration ranging from less than 6 months to 20 years. A non-significant worsening trend related to the duration of disease has also been observed [31]. Only Falsini *et al*. [54] report a correlation between PERG abnormalities and disease duration. However, this finding has not been confirmed by other authors [22,27,31]. A further impairment occurs in the presence of background retinopathy [31]. In agreement with Trick [59], our opinion is that these contradictory results may derive from different stimuli parameters used for the pattern stimulation, such as the check size and the contrast level.

There is no correlation between PERG parameters and metabolic control [22,27,29,31,54]; however a decrease in PERG maximum amplitude has been described as a consequence of acutely induced hypoglycemia [50].

The impaired PERGs observed in IDD persons with disease duration less than 6 months may be ascribed exclusively to a dysfunction of the innermost retinal layers [29]. The preganglionic elements do not contribute to this impairment because a preserved activity of the outer and middle retinal layers is suggested by the normal FERG and OP responses observed in IDD persons with a similar disease duration [30]. A contribution of preganglionic elements to the impaired PERG in IDD persons with disease duration longer than 10 years and in IDDR persons cannot be excluded, since in these persons concomitant FERG and OP abnormal responses have been observed [31].

These data suggest the presence of a dysfunction of the innermost retinal layers in IDD persons. This appears early in the course of the disease and in the absence of any signs of clinical retinopathy. These electrophysiological findings are supported by histological studies [60] in which axonal degeneration due to a dysfunction of the ganglion cell body has been observed. Examples of PERG recordings in persons with type 1 diabetes are shown in Figure 3.

Electrophysiological evaluation of the macula: focal ERG and VEP after photostress

The macular function may be evaluated by two electrophysiological tests: in 'steady-state' conditions (focal ERG) and in a 'dynamic' status during the recovery of the system after exposure to a bleaching light (VEP after photostress).

Focal ERG

Focal ERG, in response to modulated light or counterphased gratings stimulating a small central area (9°), represents a sensitive way to test layer-by-layer the function of the macular region.

The focal ERG in response to 8 Hz modulated light or counterphased gratings displays a major component at 16 Hz (second harmonic: 2F for light stimulation and 2P for pattern stimulation), while at 30 Hz modulated light a major component is at 30 Hz (first harmonic: 1F). Several

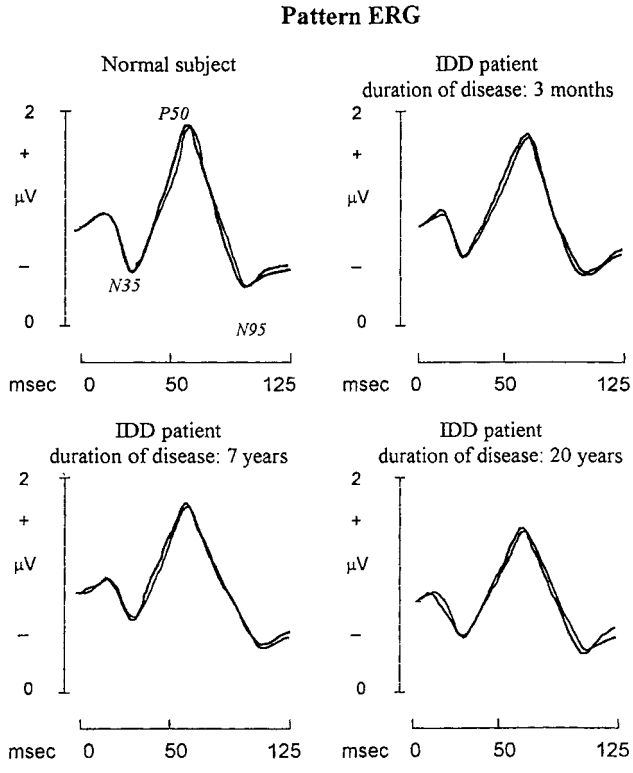

Figure 3. Examples of PERG recordings in a control subject and in persons with type 1 diabetes without retinopathy (IDD) and with background retinopathy (IDDR). In IDD with a duration of disease of 3 months and in IDD with a duration of disease of 7 years, PERG recordings show an increase in P50 implicit time and a decrease in amplitudes with respect to control subject ones. The PERG recordings are further impaired in IDDR

studies suggest different sources for Focal ERG responses: 1F is mainly receptorial in origin, 2F arises both from inner and outer retinal layers, and 2P is generated by the innermost retinal layers [13,61,62].

Recent studies have shown a decreased amplitude of 2P and 2F and a normal 1F in persons with diabetes with or without mild retinopathy. This indicates the presence in these persons of early neurosensorial alterations of the macular region, while the photoreceptor component of the central retina is not functionally involved [63,64].

The alterations of the focal ERG correlate significantly with the disease duration, but not with metabolic control [63,64].

VEP after photostress

Photostress induces VEP changes consisting of an increase in implicit time and a decrease in amplitude [14,15]. Serial recordings performed for successive 20-s periods each show, in normal subjects, a complete recovery of VEP waveform (recovery time after photostress, RT) in a range between 68 and 78 s after dazzling [65].

In IDD persons with disease duration of less than 1 year, VEPs after photostress are in the normal range [66]. In IDD persons with disease duration between 1 and 20 years, VEPs after photostress show a mean increase in P100 implicit time and a mean percentage decrement of amplitude higher than in control subjects [31]. The RT is significantly delayed in IDD persons and further delayed in IDDR persons [67]. Disease duration is not significantly related to the mean increment of P100 implicit time, to the mean percentage increase in amplitude and to the RT. An influence of the metabolic control has been suggested [31].

The abnormal VEP after photostress suggests the presence of a macular dysfunction in IDD and in IDDR persons. The results obtained by Focal ERG [63,64] indicate that, in these persons, the macular photoreceptors are unaffected and therefore the impaired VEP after photostress is likely to be due to a reduced function of the inner retinal layers of the central retina [31,66,67]. Examples of VEP after photostress recordings in persons with type 1 diabetes are shown in Figure 4.

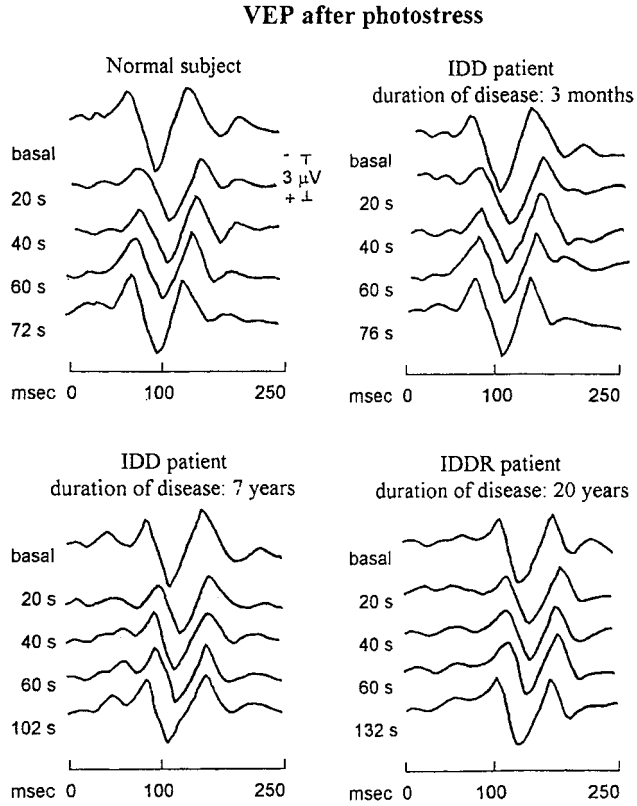

Figure 4. Examples of VEP recorded in basal condition and 20, 40, and 60 s after photostress in a control subject and in persons with type 1 diabetes without retinopathy (IDD) and with background retinopathy (IDDR). VEPs recorded in the IDD and IDDR persons at 20, 40 and 60 s after photostress show a longer P100 implicit time and a reduced amplitude compared to control subject. Note that in each recording series, the last VEP waveform is superimposable on the basal record and the corresponding time is considered recovery time (RT). In IDD persons with a duration of disease of 3 months RT is similar to that of control, while in IDD persons with a duration of disease of 7 years and in IDDR it is longer than in control subjects

Electrophysiological evaluation of neural conduction in the postretinal visual pathways: RCT and LW

Celesia *et al.* [16,17] suggest the evaluation of the postretinal neural conduction with the difference between VEP P100 implicit time and PERG P50 implicit time (retinocortical time, RCT). Marx *et al.* [68] propose a different parameter to evaluate the postretinal neural conduction by measuring the difference between VEP N75 implicit time and PERG P50 implicit time (implicit time window, LW).

The literature dealing with RCT in persons with diabetes is not conclusive, while LW has been evaluated only in newly diagnosed IDD persons. A normal RCT in persons with diabetes with little or no retinopathy has been observed by Trick *et al.* [55]. An increased RCT has been observed in persons with juvenile diabetes [27] and in IDD persons with a duration of disease shorter than 6 months [29] and in some persons with background retinopathy [59]. An increased LW has been observed in IDD persons with a duration of disease shorter than 6 months [29]. However, there is no correlation between RCT and duration of disease or metabolic control [27,29].

The increased RCT and LW indicate a delay in neural conduction between the retina and the visual cortex. It is worth noting that the increased RCT and LW observed in IDD persons with a duration of disease shorter than 6 months are not related to the impairment of PERG parameters [29]. This suggests that the innermost retinal layers and postretinal structures contribute independently to the abnormal cortical responses. Furthermore, the presence of delay in neural conduction in the

postretinal visual pathways can be also supported by the existence of correlations between VEP abnormalities, peripheral neuropathy and central conduction velocity [25].

Examples of simultaneous recordings of VEP and PERG (that allow RCT and LW to be deriveed) in persons with type 1 diabetes are shown in Figure 5.

Conclusions

In conclusion, electrophysiological tests indicate that retina, macula and visual pathways are impaired in persons with type 1 diabetes.

The earlier electrophysiological abnormal responses are recorded from the innermost retinal layers and post-retinal visual pathways, as suggested by impaired PERGs and delayed RT and LW observed in IDD persons with a duration of disease shorter than 6 months. Further electrophysiological changes are recorded from the macula (abnormal focal ERG and VEP after photostress) in IDD persons with a duration of disease greater than 1 year. Additional electrophysiological changes are recorded from the middle and outer retinal layers (impaired FERG and OPs) in IDD persons with a duration of disease greater than 10 years. All the electrophysiological tests show a worsened response in persons with type 1 diabetes when background retinopathy is present.

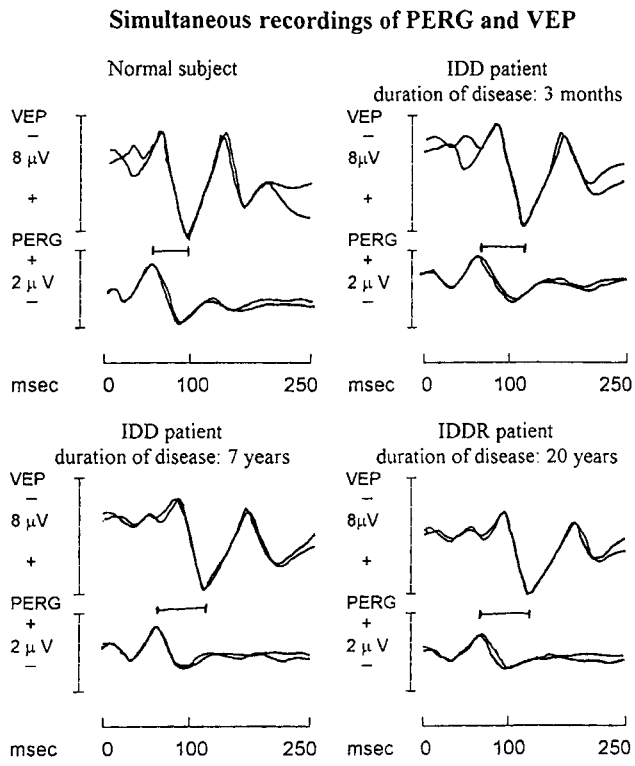

Figure 5. Examples of simultaneous recordings of VEP and PERG in a control subject and in persons with type 1 diabetes without retinopathy (IDD) and with background retinopathy (IDDR). Retinocortical time (difference time between VEP P100 and PERG P50 implicit time I__I) in IDD and IDDR persons were longer than in control subject

Short-term metabolic control, expressed by the authors as single values of HbA_{1c} or glycemia, does not seem to have practically any influence on the response to electrophysiological tests. There is no prospective data on the long-term influence of appropriate metababolic control; however it cannot be excluded that chronic hyperglycemia may contribute to the damage of the retina and optic nerve.

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