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Neural conduction in visual pathways in newly-diagnosed IDDM patients

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Abstract

Objectives: Visual evoked potentials (VEPs) show abnormal responses in newly-diagnosed insulin-dependent diabetic (IDDM) patients. Electrophysiological methods allow one to dissect and explore different structures contributing to neural conduction in the visual pathways. The aim of our work was to assess whether the VEP abnormalities are due to impaired function of the retinal layers and/or a delayed conduction in the postretinal visual pathways.

Methods: Simultaneous recordings of VEP and pattern-electroretinogram (PERG) were performed at two intervals (at entry of the study and after 3 months) in 14 newly-diagnosed IDDM patients (age: 24.8 ± 6.8 years; duration of disease: 3 ± 1.5 months), and in 14 age-matched control subjects.

Results: In comparison with control subjects, IDDM patients showed: VEP P100 latencies significantly delayed ($P < 0.01$), a significant impairment of all PERG parameters ($P < 0.01$) and retinocortical time (RCT, difference between VEP P100 and PERG P50 latencies) and latency window (LW, difference between VEP N75 and PERG P50 latencies) also significantly increased ($P < 0.01$). All electrophysiological parameters were not significantly changed when retested after 3 months. No correlations were found between VEP P100 latency, RCT, LW and PERG parameters.

Conclusions: Impaired PERG indicates an involvement of the innermost retinal layers; increased values of RCT and LW represent an index of delayed neural conduction in the postretinal visual pathways. Therefore two sources, one retinal (impaired PERG) and one postretinal (delayed RCT and LW), may independently contribute in to the abnormal responses of VEP observed in newly-diagnosed IDDM patients. Three months of relatively-stable metabolic control have not normalized the VEP and PERG impairment.

Keywords: Pattern electroretinogram; Visual evoked potentials; Retinocortical time; Latency window; Insulin-dependent diabetes; Diabetic retinopathy; Visual pathways function

1. Introduction

Visual evoked potentials (VEPs) that explore the function of the whole visual pathways are impaired in insulin-dependent diabetic patients (IDDM) patients (Puvanendran et al., 1983; Cirillo et al., 1984; Collier and Mitchell, 1985; Comi et al., 1986, 1987; Algan et al., 1989; Martinelli et al., 1991; Sartucci et al., 1993; Uccioli et al., 1993, 1995; Parisi et al., 1994, 1995a, 1997).

Electrophysiological methods allow one to explore and dissect different structures contributing to neural conduction in the visual pathways. The bioelectrical activity of the retinal layers can be evaluated by recording electroretinographic signals evoked by patterned stimuli (PERG) (Maffei and Fiorentini, 1981, 1982; Hollander et al., 1984; Maffei et al., 1985; Trimarchi et al., 1990).

An index of the neural conduction in the postretinal visual pathways expressed as 'retinocortical time' (RCT) (Celesia and Kaufmann, 1985; Celesia et al., 1986) or alternatively as 'latency window' (LW) (Marx et al., 1988) can be derived by simultaneous recordings of VEP and PERG.

The delay in VEP P100 latency observed in long-standing

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Table 1
Clinical characteristics of the patients

	Age (years)	Disease duration (months)	Exp. I BG (mg/dl)	Exp. I HbA1c (%)	Exp. II BG (mg/dl)	Exp. II HbA1c (%)
Control (n = 14)	25.8 ± 3.4	–	85 ± 6	4.2 ± 0.2	–	–
IDDM (n = 14)	24.8 ± 6.8	3.0 ± 1.5	121 ± 7	7.4 ± 0.9	119 ± 9	7.1 ± 1.3

Values are shown as mean ± SD.

IDDM patients has been ascribed to impaired functioning of the innermost retinal layers (ganglion cells and their fibers) (Porciatti and von Berger, 1983; Arden et al., 1986; Coupland, 1987; Martinelli et al., 1987, 1991; Trick et al., 1988; Boschi et al., 1989; Falsini et al., 1989; Trick, 1991; Sartucci et al., 1993), and/or to a delay of the neural conduction in the postretinal visual pathways (Trick et al., 1988; Trick, 1991; Sartucci et al., 1993).

Newly-diagnosed IDDM patients also show a delay in VEP P100 latency, but the relative contribution of the innermost retinal layer and/or of the postretinal visual pathways to this impairment has never been explored. Therefore, the aim of this work is to assess whether the delay in VEP P100 latency observed in newly-diagnosed IDDM patients could be ascribed to a dysfunction of the retinal or postretinal structures, or both. In addition, our goal is to evaluate whether these electrophysiological changes are influenced by metabolic control.

2. Methods and materials

Fourteen control subjects and 14 IDDM patients with a duration of the disease of less than 6 months were included in this study. The following criteria were required for the control subjects: normal intraocular pressure (<21 mmHg), normal visual acuity (10/10), normal visual field (Goldmann perimetry) and no ocular and/or neurological problems.

The criteria required for diabetic patients were: normal intraocular pressure (<21 mmHg) best corrected visual acuity 10/10 and absence of retinopathy evaluated by fluorescein angiography (Klein level 1) (Klein et al., 1984). The patients had not exhibited ketoacidosis or diabetic coma during the 2 months preceding the study, and glycaemia on the morning of the experiment day was less than 140 mg/100 ml. Electrophysiological evaluation was performed twice, at the beginning of the study and after 3 months. During this period the patients were followed more closely, in order to avoid major hyper- or hypoglycaemic events.

The clinical characteristics of the patients are reported in Tables 1and 2.

The protocol was approved by the local Ethical Committee and informed consent was received from each patient enrolled in the study.

All IDDM patients and control subjects underwent the following evaluations.

2.1. Simultaneous recordings of PERG and VEP

The subjects were seated in a semi-dark, acoustically-isolated room. Prior to the experiment, each subject was adapted to the ambient room light level for 10 min. Miotic or mydriatic drugs were never used. The pupil diameter of each subject was about 5 mm and similar values of pupil size in control subjects and in IDDM patients were

Table 2
Clinical and electrophysiological data in IDDM patients observed at the first examination

Obs	Age (years)	DD (months)	BG (mg/dl)	HbA1c (%)	N35 (ms)	P50 (ms)	P50 – N95 (μV)	N75 (ms)	P100 (ms)	RCT (ms)	LW (ms)
LB	39	2	115	7.5	34	61	0.5	87	113	52	26
AC	21	3	120	7.1	37	58	1.0	91	116	58	33
SF	21	3	112	7.1	38	61	0.9	90	119	58	29
TR	28	3	127	7.3	39	59	0.6	88	113	54	29
DR	23	6	116	8.6	41	62	0.7	89	116	54	27
BC	28	3	133	8.6	41	58	1.0	83	112	54	25
MG	39	2	136	7.4	38	63	1.2	88	114	51	25
RE	23	6	121	7.2	38	58	0.8	88	117	59	30
CS	18	3	115	8.8	40	61	1.2	93	119	58	32
LG	20	1	124	6.3	40	59	0.8	93	119	60	34
DA	25	3	115	7.0	38	60	0.9	89	116	56	29
TA	20	1	113	8.2	40	59	0.7	88	117	58	29
MV	18	3	124	7.1	40	61	1.2	93	119	58	32
SD	24	3	122	6.3	39	57	0.8	91	112	55	34

DD, disease duration; BG, blood glucose level; N35, P50, PERG N35 and P50 peak latencies; P50 – N95, PERG P50 – N95 amplitude; N75, P100, VEP N75 and P100 peak latencies; RCT, difference between VEP P100 and PERG P50 latencies; LW, difference between VEP N75 and PERG P50 latencies.

observed. The display was surrounded by a uniform field of luminance 5 cd/m^2.

VEPs and PERG were recorded using a previously-published method (Parisi, 1997; Parisi et al., 1997). The visual stimuli were checkerboard patterns (contrast, expressed as '$L_{max} - L_{min}/L_{min} + L_{max}$' was 95%, mean luminance 100 cd/m^2), generated on a TV monitor and reversed in contrast at the rate of 2 reversals/s. At a viewing distance of 114 cm the single check subtended a 30′ visual angle and the screen of the monitor subtended 12.5° (Celesia et al., 1986). The stimulation was monocular and applied to the right eye, after occlusion of the left eye.

2.1.1. VEP recordings

Silver/silver-chloride cup-shaped electrodes were fixed with collodion in the Oz position (active electrode), and the Fpz position (reference electrode) with the ground in the left arm. The interelectrode resistance was kept below 3 kΩ. The bioelectric signal was amplified (gain 20 000), filtered (band-pass 1–100 Hz) and averaged with automatic rejection of artifacts by BM 6000 (Biomedica Mangoni, Pisa, Italy) (200 events free from artifacts for every trial). The analysis time was 250 ms.

The transient VEP was characterized by several waves with 3 peaks, that which in normal subjects appeared after 75–100 and 145 ms. These peaks had negative (N75), positive (P100) and negative (N145) polarity, respectively.

2.1.2. PERG recordings

The bioelectrical signal was recorded by a small Ag/AgCl skin electrode placed over the lower eyelid. PERGs were derived bipolarly between the stimulated (active electrode) and the patched (reference electrode) eye, using the method previously described (Fiorentini et al., 1981). The ground electrode was in Fpz. The interelectrode resistance was lower than 3 KΩ. The signal was amplified (gain 50 000), filtered (band pass 1–30 Hz) and averaged, with automatic rejection of artifacts (200 events free from artifacts for every trial) by BM 6000. The analysis time was 250 ms.

The transient PERG response is characterized by a number of waves with 3 subsequent peaks of negative, positive, and negative polarity, respectively. In normal subjects, and in the conditions of our experiment, these peaks have the following mean latencies: 35, 50 and 95 ms.

In the recording session, simultaneous PERGs and VEPs were recorded at least twice and the resulting waveforms were superimposed to check the repeatability of the results.

We accepted PERG and VEP signals with signals-to-noise ratio >2. The noise was measured by recording the bioelectrical signals, while the monitor was screened by a cardboard and noise <0.1 μV (mean 0.085 μV) was observed in all subjects tested.

For all PERGs and VEPs the peak latency and the peak amplitude of each wave were measured directly on the displayed records by means of a pair of cursors.

RCT was calculated as the difference between VEP P100 peak latency and PERG P50 peak latency, according to Celesia et al. (Celesia and Kaufmann, 1985; Celesia et al., 1986). LW was calculated by subtracting the N75 peak latency of VEP from P50 peak latency of PERG according to Marx et al. (1988).

Examples of simultaneous PERG and VEP recordings from a normal subject and an IDDM patient are shown in Fig. 1.

2.1.3. Statistics

Results are expressed as mean ± SD. The differences between the IDDM patient group and the control subject group were evaluated by one-way analysis of variance for repeated measures (ANOVA). Linear regression was used to assess the correlation between PERG parameters and VEP P100 latency, RCT and LW, and between electrophysiological and metabolic control parameters. In ANOVA and linear regression a P value less than 0.05 was considered significant.

3. Results

3.1. VEP

Data are shown in Fig. 2.

In controls, VEP, N75 and P100 latencies were within our normal limits, expressed as mean value ± 3SD (Parisi et al., 1995b).

VEP, N75 and P100 latencies were significantly delayed in the IDDM patient group when compared with the control subject group ($P < 0.01$). At the second experiment, performed after 3 months, N75 and P100 latencies were unmodified.

3.2. PERG

Data are presented in Figs. 3 and 4.

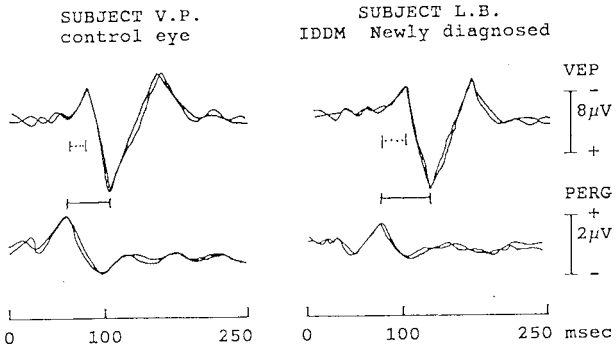

Fig. 1. Examples of simultaneous recordings of VEP and PERG of subjects VP (control eye) and LB (IDDM eye). IDDM patient showed a delay in VEP P100 and PERG P50 latencies, and a reduced PERG amplitude. Retinocortical time (difference time between VEP P100 latency and PERG P50 latency, |——|) and latency window (difference between VEP N75 latency and PERG P50 latency, |.....|) in IDDM patient was longer than in control subject.

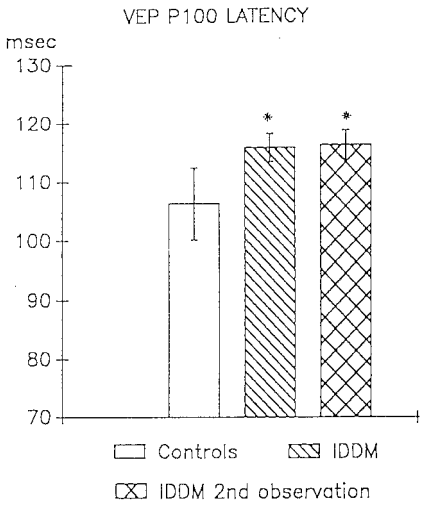

Fig. 2. Histogram of mean values of VEPs P100 latency. *$P < 0.01$ versus control eyes.

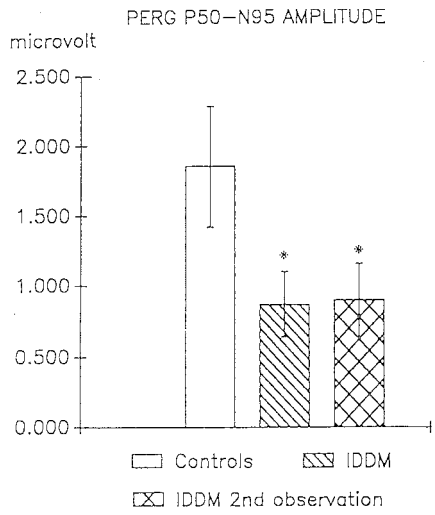

Fig. 4. Histogram of mean values of PERG P50 – N95 amplitude. *$P < 0.01$ versus control eyes.

In control subjects, the PERG parameters (N35 and P50 peak latency and P50 – N95 amplitude) were within normal limits expressed as mean value ± SD for P50 – N95 amplitude, and mean value ± 3SD for P50 latency (Parisi et al., 1995b).

In the IDDM patient group N35 and P50 peak latencies were significantly higher than in the control subject group ($P < 0.01$); P50 – N95 amplitude was significantly lower than in the control group ($P < 0.01$); and no correlations were found between PERG parameters and VEP P100 latency (see Table 3). After 3 months, PERGs performed in IDDM patients showed unchanged results.

3.3. RCT and LW

Data are presented in Fig. 5.

RCT and LW were significantly higher in the IDDM patient group than in the control subject group ($P < 0.01$), at the first and the second experiment.

In IDDM patients, no correlations were found between PERG parameters (N35 and P50 latency, P50 – N95 amplitude) and RCT and LW (see Table 3); furthermore, no correlations were found between the electrophysiological parameters and the parameters of metabolic control (see Table 4).

4. Discussion

The newly-diagnosed IDDM patients tested in this study showed a delay in VEP P100 latency, confirming our previous results obtained in other newly-diagnosed IDDM patients, in which electrophysiological tests were performed using a different recording apparatus (Caldwell 7400

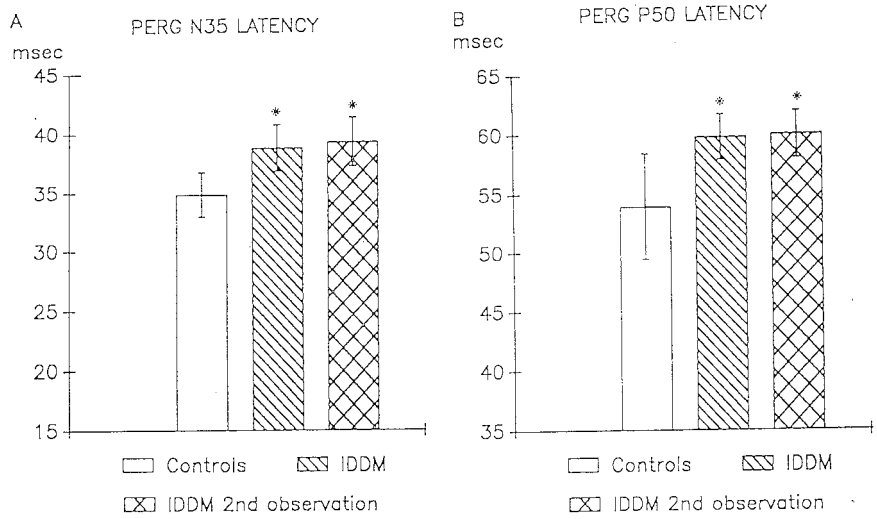

Fig. 3. Histogram of mean values of PERG parameters. (A) N35 latency. (B) P50 latency. The vertical lines represent one standard deviation. *$P < 0.01$ versus control eyes.

Table 3

Regression analysis and correlation between PERG parameters and VEP P100 latency, RCT and LW

Vs	VEP P100 latency	RCT	LW
N35 latency (ms)	$r = 0.228$	$r = 0.275$	$r = 0.144$
	$t = 0.813$	$t = 0.991$	$t = 0.503$
	$P = 0.432$	$P = 0.341$	$P = 0.624$
P50 latency (ms)	$r = 0.272$	$r = -0.376$	$r = -0.468$
	$t = 0.981$	$t = -1.408$	$t = -1.834$
	$P = 0.346$	$P = 0.185$	$P = 0.092$
P50 – N95 amplitude (μV)	$r = 0.346$	$r = 0.166$	$r = 0.142$
	$t = 1.272$	$t = 0.582$	$t = 0.495$
	$P = 0.226$	$P = 0.572$	$P = 0.629$

Table 4

Regression analysis and correlation between electrophysiological data and metabolic control parameters observed at the first examination

Vs	Blood glucose	HbA1c
PERG N35 latency (ms)	$r = 0.214$	$r = 0.353$
	$t = 0.759$	$t = 1.308$
	$P = 0.463$	$P = 0.215$
PERG P50 latency (ms)	$r = -0.055$	$r = 0.316$
	$t = -0.190$	$t = 1.153$
	$P = 0.853$	$P = 0.271$
PERG P50 – N95 amplitude (μV)	$r = 0.352$	$r = 0.116$
	$t = 1.301$	$t = 0.406$
	$P = 0.218$	$P = 0.692$
VEP N75 latency (ms)	$r = -0.309$	$r = -0.394$
	$t = -1.126$	$t = -1.484$
	$P = 0.282$	$P = 0.164$
VEP P100 latency (ms)	$r = -0.461$	$r = -0.021$
	$t = -1.801$	$t = 0.072$
	$P = 0.097$	$P = 0.944$
RCT (ms)	$r = -0.409$	$r = -0.222$
	$t = -1.554$	$t = -0.787$
	$P = 0.146$	$P = 0.446$
LW (ms)	$r = -0.244$	$r = -0.529$
	$t = -0.871$	$t = -2.162$
	$P = 0.401$	$P = 0.052$

instead of BM 6000) (Parisi et al., 1995a; Uccioli et al., 1995). VEPs explore the whole visual pathways from photoreceptors to visual cortex; however, they do not reveal the relative contributions given by the different structures involved in visual function. We have evaluated the function of the retinal layers (PERG recordings) and the postretinal neural conduction (RCT and LW), in order to assess their contribution to the genesis of VEP P100 latency delay.

Newly-diagnosed IDDM patients show an impairment of all PERG parameters.

PERG reflects the bioelectrical response of the innermost retinal layers to visual stimuli represented by gratings or checkerboard alternated in contrast. In fact it has been clearly shown (Maffei and Fiorentini, 1981) that PERG is related to the activity of ganglion cells and their fibers: in experimental animals the resection of the optic nerve with the consequent retrograde degeneration of ganglion cells and their fibers is followed by the disappearance of PERG (Maffei and Fiorentini, 1982; Hollander et al., 1984; Maffei et al., 1985; Trimarchi et al., 1990).

Extensive literature has been produced on PERG in diabetic patients with or without retinopathy. In diabetic patients without retinopathy the data are controversial: some authors observed PERG in the normal range (Wanger and Persson, 1985; Coupland, 1987; Hardy et al., 1995), while others recorded pathological values (Trick et al., 1988; Trick, 1991; Pragar et al., 1990; Parisi et al., 1997), even in patients with only 3.5 years of duration of disease (Falsini et al., 1989; Caputo et al., 1990; Ghirlanda et al., 1991). Mild-to-moderate retinopathy is characterized by pathological results of all PERG parameters (Arden et al., 1986; Coupland, 1987; Boschi et al., 1989; Ghirlanda et al., 1991).

The impaired PERG observed in our newly-diagnosed IDDM patients may be ascribed exclusively to a dysfunc-

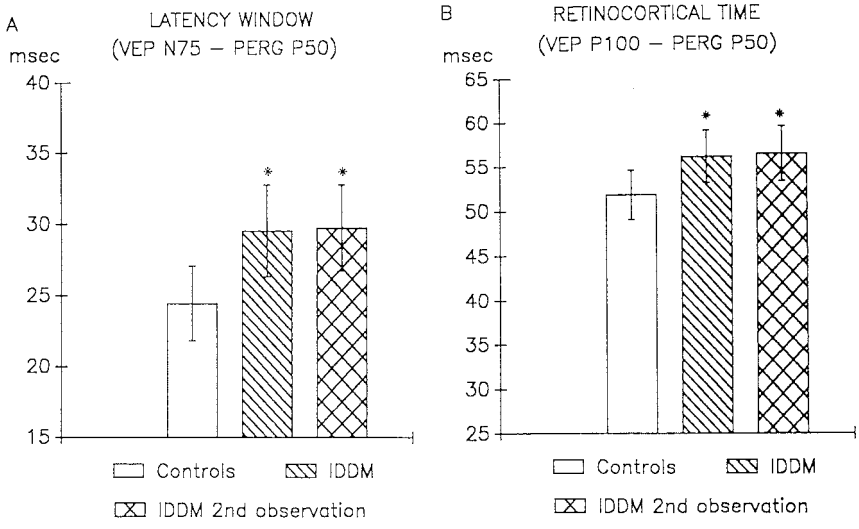

Fig. 5. Histogram of the mean values of LW (A) and RCT (B). *$P < 0.01$ versus control eyes.

tion of the innermost retinal layers. The preganglionic elements do not contribute to this impairment, because preserved activity of the outer and the middle retinal layers is suggested by the normal flash-ERG and oscillatory potential responses observed in our previous work (Uccioli et al., 1995) in newly-diagnosed IDDM patients.

Newly-diagnosed IDDM patients show increased RCT and LW.

RCT represents an index of postretinal neural conduction, as suggested by previous works performed in patients with maculopathies and optic nerve demyelination. Patients with maculopathies show increased PERG and VEP latencies, and unmodified RCT, suggesting an increasing latency only at the retinal level (Celesia and Kaufmann, 1985). Patients with optic nerve demyelination present normal PERGs, delayed VEPs and prolonged RCT, suggesting a delay in the postretinal pathways (Celesia et al., 1986).

Some criticisms might be addressed to RCT. It is unlikely that RCT represents the real transit time of neural conduction between retina and visual cortex; we do not believe that the bioelectrical signals takes 50 ms to travel from the retina to the visual cortex in normal subjects, as found by ourselves in this experiment, and previously reported by Celesia et al. (1986). Due to these concerns, we have considered also the LW of Marx et al. (1988), which is an additional index of neural conduction in the postretinal visual pathways, much shorter than the RCT. However both of these indices, RCT and LW, were similarly impaired in newly-diagnosed IDDM patients.

The literature dealing with RCT in diabetic patients is not conclusive. In fact, increased RCT in patients with juvenile diabetes has been observed (Sartucci et al., 1993); increased RCT in some patients with background retinopathy, and a normal finding in diabetic patients with little or no retinopathy has been found (Trick et al., 1988; Trick, 1991). LW has never been evaluated in IDDM patients.

The increased RCT and LW observed in newly-diagnosed IDDM patients reveals the presence of a delayed neural conduction between the retina and the visual cortex.

In conclusion, in newly-diagnosed IDDM patients, two factors may contribute to the VEP P100 latency delay: one related to the innermost retinal layers dysfunction as suggested by abnormal PERG, and one related to an impairment of the neural conduction at postretinal level as indicated by the delay of RCT and LW. The absence of correlations between the PERG parameters and RCT and LW suggest that the innermost retinal layers and postretinal structures contribute independently to the VEP P100 delay.

Some additional considerations also derive from our data. Electrophysiological parameters could be influenced by metabolic control, and the metabolic derangement that might still be present in newly-diagnosed IDDM patients when tested, could influence the results.

In order to minimize these influences, we performed the electrophysiological tests only when the blood glucose was less than 140 mg/dl on the day of the experiment. In addition, we repeated the tests 3 months later, after a period of a relatively stable metabolic control (no major hyper- or hypoglycaemia).

Indeed, the electrophysiological parameters did not correlate with BG and HbA1c and were not influenced by 3 months of relatively stable metabolic control.

However, we still do not know whether the normalization of BG may influence electrophysiological parameters, because the absolute values of BG and HbA1c did not change significantly between the first and second experiments, and remained above the normal range.

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