Visual and Auditory Long-latency Brain Potentials in Patients with Type 2 Diabetes Mellitus

Oscar Hernando Hernández¹,², Luisa Aguirre-Manzo¹, Víctor Monteón¹, Ruth López Guadalupe Maldonado-Velázquez³

²Centro de Investigaciones Biomédicas, Universidad Autónoma de Campeche. San Francisco de Campeche, México.
³Facultad de Ciencias Químico-Biológicas, Universidad Autónoma de Campeche. San Francisco de Campeche, México.

*Corresponding Author: Oscar Hernando Hernández

Abstract

Purpose Diabetes mellitus type 2 (DM2) selectively affects the sensory systems causing damage to some cognitive brain processes. Since complications deteriorate the quality of life, it is imperative to find new preclinical indicators of neurodegenerative changes, identifying which parameter and sensory modality is more sensitive to the disease to monitor them directly. In this study, parameters of visual and auditory long-latency brain potentials (P200) were compared in order to determine their characteristics and its possible associations with the metabolic status of patients. Materials/methods Sensory stimuli were applied to 36 patients and 36 controls, and the latency, amplitude and the rate of rise of the P200 waves were measured. Results The amplitude of visual potentials showed an inverse relationship with Glycemia (p < 0.038, 1-tailed) and glycosylated hemoglobin (p < 0.040), while the rate of rise was lower in >10-year diabetic patients (p < 0.023). Latencies and auditory parameters were more resilient. No differences between groups were obtained. Conclusions there is evidence that DM2 produces selective effects on the P200 wave, which are dependent on the parameter and the sensory modality measured. It is suggested to use the amplitude and the rise rate of visual potentials to monitor neurological impairment in uncontrolled patients.

Keywords: Diabetes Mellitus Evoked Potentials, Auditory, Visual, P200.

Introduction

Diabetes Mellitus type 2 (DM2) produces frequent complications in different systems of the organism [1, 2]. It is common to see patients with disorders of leg sensitivity or poor vision, who end up amputated or blind. [3-5].

However, deafness or olfactory or taste disorders are less frequent [6], suggesting that DM2 does not affect the different sensory systems alike. Electrophysiological studies indicate that there is a differential sensitivity of neurons to disease, with sensory and peripheral fibers being more sensitive than motor and central fibers [7]. Measurement of averaged brain waves has allowed us to advance in the understanding of how DM2 affects neural pathways although there are many controversial results. The most frequently brain waves studied are the sensitive wave P100 to visual stimuli, and the cognitive wave P300 evoked by visual or auditory stimuli. Numerous evidences indicate that there is a significant increase in the latency of P100 [7-23] and of P300 [6, 24-31] in diabetic patients compared to controls.

However, there are also reports where these effects have not been observed [32, 33]. With respect to the amplitude, which is the other parameter most used in the analysis of brain waves, controversial results have been reported. Some investigators have observed a reduction in the amplitude of P100 [11,12,14,16-19,22,33] or P300 [28-30] of patients, while others have not found
Some papers report an association between the latency or amplitude of these waves with the metabolic state of the patients [6,14,15,19,26,28] or with the duration of the disease [10,11,13,14,16,18,20,21,23]. Other researchers report that no association exists [7, 8, 12, 22, 24, 25, 27, 29-33]. These discrepancies reveal the need to find more reliable and robust parameters of possible neural damage at the central level using non-invasive methods. A good possibility is to measure the set of three parameters (rate of rise, amplitude and latency) of the cognitive wave P200. The P200 is a long latency endogenous potential recorded on the vertex and generated in the frontal associative cortex [35, 36], with cognitive functions related to attention and habituation [37-39]. Its underlying neural generators are independent to those that generate other brain potentials like the P300 [37]. It was recently shown that P200 is dependent on the sensory modality and the parameter used to measure it [39]. P200 rate of rise has been reported to be more sensitive than latency and amplitude to habituation and to the effect of neuroactive substances such as alcohol [38].

Very few researches have studied the P200 in diabetic patients. In auditory tasks no differences were found between diabetics and controls in the amplitude and latency parameters [24]. The unique previous report about P200 measuring the rate of rise, amplitude and latency, used somatosensory stimuli, where negative associations of rising rate or amplitude with glycosylated hemoglobin were observed in patients [40]. There is no antecedent measuring such three parameters when applying visual and auditory stimuli in diabetic patients. It is unknown to what degree such parameters are affected and if there is any relationship with the patients' metabolic state or disease duration.

Since DM2 complications deteriorate the quality of life, it is essential to find new pre-clinical indicators of neurodegenerative changes, identifying which parameters and sensory systems are more sensitive in order to monitor them more directly. Therefore, the purpose of this research was to extend our previous studies in DM2 patients comparing the P200 rate of rise, amplitude and latency between diabetics and controls, applying visual and auditory stimuli, and to determine if there is any association between metabolic control and duration of the disease with the electrophysiological parameters.

**Materials and Methods**

**Participants**

An observational, prospective, cross-sectional and analytical study was presented with 72 participants: 36 adult patients diagnosed with DM2 and 36 subjects without diabetes or some other chronic-degenerative disease that served as a control group (Cntrl). The patients were known from the Department of Internal Medicine of the General Hospital of Specialties (GHS) of Campeche. All had at least one year of diagnosis and no complications from diabetes or any other systemic, chronic or degenerative disease. The controls were selected from the relatives or companions of patients when they went to the outpatient clinic and showed fasting glucose levels below 100 mg/dL.

Patients or controls with drug addiction, pregnant or post-menopausal women with hormone replacement therapy were excluded, or in whom electrophysiological studies were contraindicated for any cause. This research adheres to the international principles of research ethics postulated in the Helsinki Declaration of 1975 (2008 revision) preserving the confidentiality of the data and the identity of the participants, who agreed to sign the letter of informed consent, after they have received a comprehensive explanation of the study. The protocol was previously reviewed and approved by the GHS Research Ethics Committee.

**Evaluations and Instruments**

**Biochemical Evaluation**

Fasting participants were given a blood sample from the brachial vein using a conventional Vacutainer® technique for the determination of glycemia (Gly) and glycosylated hemoglobin (HbA1c, only to patients).

**Electrophysiological Evaluation**

**Stimulation**

The Viking Quest System® equipment was used to obtain the P200 waves by applying visual or auditory stimuli at a frequency of 1
per second, for each sensory modality. The auditory stimuli were 10-ms clicks applied bilaterally through headphones. The auditory threshold was determined by gradually increasing the intensity of the stimulus from zero until obtaining its minimum perception. The voltage obtained was adjusted to 20 times the threshold, which corresponded to 50 ± 1.8 dB in total. The visual stimuli were presented to both eyes through a monitor with white and black boxes, type "chessboard", which are reversed with each stimulus. The angle of the visual arc was 10.3 ° with a luminescence of 17 candela per square meter (cd/m²) and a contrast of 90%.

Recordings

The data were recorded using the Viking Quest® and analyzed "offline". Disc electrodes (Grass F-E5H) were attached to the scalp, with the active electrode in Cz, the reference in the left earlobe and the ground in both ears (10-20 international system) [38, 39]. The impedance level was kept below 5kΩ. At the beginning of the record session, each patient was asked to count the stimuli (visual or auditory) and to remain still. Three averages were obtained, each of 64 stimuli. The second sensory modality was then evaluated, also obtaining three averages, with intervals of 1-2 minutes between trials for rest of the patient. The sensory order was counterbalanced across participants. Thus, three potentials averaged in each sensory modality were obtained applying a total of 384 stimuli per patient and 27648 in the total sample (N = 72). Records with motion artifacts were automatically discarded by the system.

Corrective lenses were allowed for visual testing. Three parameters were measured in each P200 wave: peak latency (ms), peak-to-peak amplitude (μV) and rate of rise (μV / ms). Latency is the time to peak in the interval 120-250 ms from the time of application of the stimulus. The amplitude is the wave size measured from N1 to the peak of P200. The rise rate represents the regression coefficient that describes the μV per unit change in milliseconds and calculates the slope of the line crossing the selected area, ranging from N1 to the peak of P200.

Procedure

Participants were summoned at 8:00 a.m. in fasting. Patients were accompanied by a support person. A brief reminder was given of the protocol procedures, weight, height and vital signs were recorded and the blood sample was taken to determine HbA1c and/or Gly levels. They were then placed in the area of electrophysiological studies. At the end of the tests, they were sent to the common waiting area or to the exit. Patients were given an energy drink (Glucerna®).

Statistical Analysis

Using the SPSS v.22 software, a univariate descriptive statistical analysis was performed with mean values and standard deviation or standard error. The normality of the distribution was verified by the Kolmogorov-Smirnov test and the homogeneity of variances by the Levene test. If necessary, the logarithmic conversion was used to adjust the variables to a normal distribution and to use parametric methods. We used analysis of variance (ANOVA) with 2 (Group) x 2 (Sensory Modality) for each of the parameters of the P200 wave.

The Eta-square partial value ($\eta^2$) provided the size of the ANOVA effect. Differences between sensory systems in each group were analyzed with t-Student for related samples and the differences between groups using t-Student for independent samples, with a 95% confidence interval. Cohen's $d$ calculated the size of the effect. Spearman's bivariate correlations were used to determine possible associations between variables. Statistical significance was set at p values below 0.05. In some analyzes, a unidirectional p was used to fit the predetermined hypothesis.

Results

Thirty-six adult patients with DM2 and 36 control subjects were studied. The total sample (N = 72) had an average age of 49.6 ± 8.1 years. The DM2 group presented 51.1 ± 7.4 years and the control group 48.2 ± 8.7 years, with no significant differences (p > 0.146). There were no group differences in body mass index (DM2: 30.3 ± 5.5 kg/m², Cntrl: 28.7 ± 4.6 kg/m², p > 0.191) and mean arterial pressure (DM2: 96.4 ± 8.8 mmHg, Cntrl: 95.7 ± 16.6 mmHg, p > 0.811). Thirty-nine (54.2%) participants were male and 33 (45.8%) female. Patients had an average disease time of 10.4 ± 6.1 years, with glucose levels of 176.6 ± 85.6 mg/dL and glycosylated hemoglobin (HbA1c) of 9.1 ± 2.3%. In the first instance, the data were subjected to analysis of variance (ANOVA) using 2 (Group) x 2 (Sensory Modality) for each of the parameters of P200. In order to obtain normal distribution, the data were transformed to
logarithm base 10. In the latency, the results showed significant effects in Sensory Mode (F1,70 = 177.0, p<0.0001, η² = 0.728), where the responses with Auditory stimuli were faster (152.1 ± 2.2 ms) than those with visual stimuli (194.5 ± 2.3 ms). No effects were obtained in Group (p>0.219) or in interaction (p>0.209). Similarly, in the amplitude, effects were obtained in the sensory modality (F1,70 = 11.4, p<0.001, η² = 0.142), but not in Group (p>0.528) or in interaction (p>0.475). The responses with auditory stimuli were larger (5.51 ± 0.26 µV) than those of the visual stimuli (4.64 ± 0.30 µV). There were no effects on the rate of rise in Sensory Mode (p>0.509), Group (p>0.855) or interaction (p>0.471).

Fig. 1 shows the latency and amplitude values of both sensory modalities separated by groups. It can be observed that the pattern obtained in the control subjects, where the auditory potentials are faster and greater than the visual ones, is maintained in diabetics. The absence of significant effects (p>0.05) between groups for each electrophysiological variable was confirmed by t-Student for independent samples with the converted data. Table I shows the mean and standard deviations of the parameters of each sensory modality in both groups.

![Fig. 1: Average latency (A) and amplitude (B) of P200 of both sensory modalities separated by groups. Auditory stimuli evoked waves that were faster and larger than visual ones, both in the control group and in the diabetic group (DM2). Vertical bars represent the standard error of the mean. * P <0.003, ** p <0.0001, *** p <0.044 1-tail](image)

<table>
<thead>
<tr>
<th>Sensory Modality</th>
<th>Parameter</th>
<th>Control M (SD)</th>
<th>DM2 M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VISUAL</td>
<td>Latency (ms)</td>
<td>194.6 (18.6)</td>
<td>194.4 (18.8)</td>
</tr>
<tr>
<td></td>
<td>Amplitude (µV)</td>
<td>4.63 (2.46)</td>
<td>4.66 (2.50)</td>
</tr>
<tr>
<td></td>
<td>Rate of rise (µV/ms)</td>
<td>0.118 (0.052)</td>
<td>0.110 (0.038)</td>
</tr>
<tr>
<td>AUDITORY</td>
<td>Latency (ms)</td>
<td>148.1 (17.9)</td>
<td>155.7 (18.3)</td>
</tr>
<tr>
<td></td>
<td>Amplitude (µV)</td>
<td>5.54 (1.75)</td>
<td>5.39 (2.59)</td>
</tr>
<tr>
<td></td>
<td>Rate of rise (µV/ms)</td>
<td>0.121 (0.047)</td>
<td>0.118 (0.053)</td>
</tr>
</tbody>
</table>

The possibility that the electrophysiological parameters were related to the metabolic state of the patients, or the time of evolution of the disease, was explored through bivariate...
correlations of Spearman for each sensory modality. It was observed that only the amplitude of the visual potentials was negatively correlated with both blood glucose levels (Fig. 2) and glycosylated hemoglobin levels (HbA1c, Fig. 3). There were no correlations of the other electrophysiological variables with glycemia or HbA1c levels. Nor with the time of illness, however, when dichotomizing this variable with a cut-off point at 10 years, significant differences were observed in the rate of rise of visual potentials (Fig. 4). Patients with 10 or more years of diagnosed presented waves with a lower rate of rise than those with less than 10 years. 1.1% of the total electrophysiological records were discarded because they presented amplitudes beyond the range of ± 50 μV in the segment from 120 to 250 ms post-stimulus, and corresponded to noise artifacts.

![Fig. 2: Spearman correlation between the amplitude of P200 wave evoked with visual stimuli and blood glucose values of patients. The solid downward line indicates the least squares regression fit](image1)

![Fig. 3: Spearman correlations between P200 wave amplitude evoked by visual stimuli and glycosylated hemoglobin (HbA1c) values of patients. The solid downward lines indicate the least squares regression fit](image2)

![Fig. 4: Rate of rise of averaged visual P200 waves separated by time with diabetes mellitus (DM2). <10 means less than ten years; > 10 means ten or more years. Those with the longest time of DM2 presented a lower rate of rise of the potentials. The vertical bars represent the standard error of the mean. * P <0.023; Cohen’s d: 0.825](image3)
Discussion

The most relevant finding obtained in this study was that the effects of diabetes on the cognitive wave P200 depend on the sensory modality and the parameter used, observing that lower amplitude of the visual P200 correlated with higher glycemia or HbA1c values. Also the rate of rise of visual modality showed a significant reduction in diabetics with more than 10 years with the disease. On the contrary, no effects were observed in visual latency or in the auditory parameters. These effects are congruent with those found in short-latency evoked potentials of diabetic patients, obtaining more important changes in the visual than in the auditory waves [7].

Although most studies correlate latency with disease duration [10,11,13,14,16,18,20,21,23], or with the metabolic deterioration of patients [6,14,15,19,26,28], in this study the amplitude of the visual modality was the most sensitive parameter to high levels of glycemia and HbA1c. Also the rate of rise of the visual system was the most sensitive measure associated to the chronicity of the disease.

The amplitude sensitivity of the visual waves from biochemically impaired patients is

Similar to that reported for somatosensory potentials and is congruent with greater cognitive deterioration [40]. Since amplitude and rate of rise reflect the number of synchronized active neurons and their recruitment dynamics respectively, the reduction of these parameters in chronic and metabolic deteriorated patients may reflect the toxic effects of long-lasting hyperglycemia on visual cells, since a persistent increase of blood glucose increases the enzymatic activity, vascular endothelial growth factor, oxidative stress, the presence of free radicals and the release of inflammatory cytokines, all of which generates vascular lesions and neural ischemia [41,42].

Further studies are needed to understand the involvement of peripheral neurons from retina or optic nerve in central evoked potentials, because one of the most frequent complications in diabetic patients is retinopathy [2, 43]. This is the first study where three parameters (latency, amplitude and rate of rise) of the P200 wave are reported when applying visual and auditory stimuli in the same patients. It corroborates previous data obtained in healthy subjects where the P200 elicited with auditory stimuli occurs with lower latency and greater amplitude than the visual P200 [39]. This response pattern showed no change in diabetic patients.

The absence of group differences obtained here is comparable and congruent to Takeda’s et al., work [24] measuring the auditory P200 wave. The small but significant increase in the P200 latency of DM2 patients applying somatosensory stimuli obtained previously by our lab [40] was not observed here for visual and for auditory modalities. This difference suggests that some demyelinating or axonal degeneration effects may selectively affect some sensory or cognitive pathways without affecting others [44].

Although the latency and amplitude are the most common measures used in averaged brain potentials, the rate of rise measure was added here because this parameter provides a dynamic description of a wave (in µV/ms) and provides a better idea of the shape of the wave. Besides, the rate of rise can provide additional information that amplitude or latency measures do not see. Examples of this are that the rise rate of the P200 wave was more sensitive than the amplitude and latency to high HbA1c levels of diabetic patients [40] and the lower rise rate found in diabetic patients with more than 5 years with the disease observed in this research. Then, the rate of rise is a useful parameter that should be included in the analyses of averaged brain potential experiments.

Although the effects of diabetes on P200 parameters were clear, it is advisable to corroborate them with a larger sample size and extend them to specific age or gender groups or to patients with type 1 diabetes or other co morbidities. The realization of new studies with similar results, using P200 parameters will reinforce its use and benefit in the monitoring of diabetic patients, with the bonus of being a noninvasive technique that allows the repeated evaluation of each patient without damaging it. Since cognitive impairment in diabetic patients is evident [35,44-46], it would be desirable to study some of these functions, particularly habituation [38,39], using the amplitude and the rate of the rise of P200 with visual or somatosensory
stimuli [40], because they have been shown to be very sensitive to the disease. The monitoring of patients using evoked potentials, using the appropriate parameter and sensory system, will allow the clinician to follow the cerebral (sensory / cognitive) changes that the disease produces and can establish better therapeutic measures, in order to avoid or delay the appearance of complications [2].

Conclusions

In conclusion, this paper presents evidence that DM2 produces selective effects on the cognitive wave P200, which are dependent on the measured parameter and the sensory modality used. The amplitude and the rate of rise of visual waves are sensitive to hyperglycemia and duration of the disease respectively, and can be used to monitor the subclinical changes and the neurological deterioration that occurs in diabetic patients. On the other hand, the measurement of P200 latencies or parameters of the auditory waves is less advisable. The need to maintain patients with adequate blood glucose levels is emphasized, as the metabolic decontrol involves neuronal and cognitive damage, evidenced by P200 waves with smaller amplitude or lower rise rate.

Acknowledgments

This project was partially funded by the FOMIX CONACYT-GOVERNMENT OF THE STATE OF CAMPECHE No. 0170573, Secretaría de Salud and the Universidad Autónoma de Campeche.

References


44 E Reske-Nielsen, K Lundbaek (1968) Pathological changes in the central and peripheral nervous system of young long-term diabetics. II. The spinal cord and peripheral nerves. Diabetologia, 4:34-43.
