Neuroendocrinology Letters ISSN 0172–780X

ORIGINAL ARTICLE

Event related P300 potential in NIDDM patients without cognitive impairment and its relationship with previous hypoglycemic episodes

Miguel N. Hissa, José Artur C. D'Almeida, Fernanda Cremasco & Veralice M. S. de Bruin
Department of Clinical Medicine, Federal University of Ceará, Fortaleza, Brazil.

Correspondence to: Dr. Veralice M. S. de Bruin
Departamento de Medicina Clínica, UFC,
Rua Prof. Costa Mendes 1608 4º Andar,
CEP 60430-140 Fortaleza, CE, BRAZIL.
TEL: +55 85 2888052
FAX:+55 85 2346819
E-MAIL: debruin@ivia.com.br

Submitted: *February 11, 2002*
Accepted: *February 25, 2002*

Key words: **P300; diabetes; NIDDM; retinopathy; hypoglycemia; nervous system**

*Neuroendocrinology Letters 2002; **23**:226–230 pii: NEL230302A04*

Abstract

OBJECTIVES: The purpose of this study was to evaluate the ERP P300 in non insulin dependent diabetes mellitus (NIDDM) patients without cognitive impairment and the relationship with clinical variables, the presence of retinopathy and previous hypoglycemic episodes.

METHODS: NIDDM patients (N=44) without evidence of cognitive impairment and controls (N=17) were studied clinically and with ancillary exams and the ERPs P300 were recorded. Patients were examined clinically and with the Folstein Mini-Mental Examination (MMSE) for cognitive function and all patients showed a score higher than 26 (maximal value=30). Previous hypoglycemia was evaluated through a questionnaire establishing the number of episodes and the symptoms of hypoglycemia in a scale scoring from zero to 15.

RESULTS: ERP P300 latencies were significantly higher in NIDDM patients than in controls ($p<0.03$). ERP P300 measures were significantly related to age (Pearson, $p<0.01$) and not to metabolic variables, disease duration or the presence of retinopathy. Severity of hypoglycemia was not associated to ERP P300 latency.

CONCLUSIONS: Our study supports the evidence that NIDDM patients, without signs of nervous system involvement, have ERP P300 alterations and this is not related to retinopathy, metabolic variables or previous hypoglycemic episodes. Chronic hyperglycemia may alter brain glucose transport and increase tolerance to hypoglycemia effects in the nervous system.

ABBREVIATIONS:

ERP P300	Evoked related potential P300
NIDDM	Non-insulin-dependent diabetes mellitus
NS	Nervous system
MMSE	MiniMental State Examination
CT	Cranial tomography
EKG	Electrocardiogram
dB	decibels
Hz	Hertz
Ms	millisecond
Fz	frontal reference
Cz	central reference
Pz	posterior reference
KΩ	kiloohms

Introduction

The chronic course of diabetes is frequently associated to severe nervous system (NS) complications such as brain hemorrhages, ischemia associated to vascular pathology, peripheral and autonomic neuropathy [1,2,3]. More subtle changes in the central NS can frequently move forward without perception [4]. Chronic hypertension, high cholesterol level, cardiac dysfunction and toxic effects of hyperglycemia are some factors contributing to central NS alterations [5,6,7]. Other factors as disease duration, age, exercise and co-morbid conditions may influence cerebral complications and cognitive function [8,9,10].

The optimum control of diabetes has been recommended in an attempt to prevent or delay microvascular and neuropathic complications [11]. Hyperglycemia has been associated to increased cerebral damage in stroke [12] and on the other extreme, it is well established that states of hypoglycemia can induce severe brain damage [13,14,15]. Adding further controversy to the subject, evidences indicate that chronic hyperglycemia can alter brain glucose transport and tolerance to hypoglycemia [16,17,18]. Previously, studies indicate that episodes of hypoglycemic coma have not always been associated to permanent impairment of cognitive function in IDDM patients [19,20,21]. Cognitive function can be slowly and unrecognizably impaired in assymptomatic adults and recently, with increasing more strict controls of glucose levels, it is important to understand if deterioration of cortical function will prevail over time.

Event-related potential (ERP) P300 auditory evoked potential measure reflects the speed of neural events related to attention and short term memory [22,23,24]. Increase in ERP P300 latency has been associated to abnormalities in psychometric tests in diabetic patients [23,24]. Recognizing assymptomatic cerebral dysfunction and the modifiable risk factors influencing cognitive changes can put forward preventive treatment in diabetes. To verify undetected NS involvement in diabetic patients, we studied the measure of ERP P300 latency and its relationship to clinical and metabolic variables.

Material and methods

We have studied a population of diabetic patients without clinical evidences of cognitive impairment or cerebral dysfunction. Inclusion criteria were good control of diabetic conditions, no previous history of neurological events, cardiovascular complications or signs of brain damage on CT scan. Patients from fifth to seventh decade independent of gender were included. The use of medications as sedatives, antidepressives or neuroleptics was considered an exclusion criterium. Patients with history of recent infectious disease were also excluded. Most individuals were on regular insulin therapy or on oral hypoglycemic drugs for diabetic control. A clinical examination for cognitive function and a Brazilian version of the Minimental State Examination (Folstein) (MMSE) were performed. All patients included in the study had normal cognitive function and a score above 26 (maximal value=30). Ancillary tests for diabetes and metabolic function were performed before testing. Cardiac function was established as normal after clinical and EKG examination in all individuals. There were no peripheral signs of vascular or neural pathology. Patients were tested through ophthalmoscope examination for the presence of retinopathy. Patients were questioned whether they had any episodes of hypoglycemia and whether they needed any help during the episodes. NIDDM patients were grouped according to having none (group 1), less than five (group 2) or more than five (group 3) hypoglycemic episodes. A scale scoring from 0 to 15 about hypoglycemic symptoms (Table I) was also used for evaluation. Both types of evaluation were used to compare with P300 measures.

The ERPS were recorded with Neuropack Σ Evoked Potential Measuring System (Nihon Kohden).

Blood tests were all performed within 8 days of ERP P300 measure. Hearing was evaluated before testing and the stimuli at 40 dB normal hearing level, used in the present study, were sufficient in sensation levels for

Table I . Questionnaire of severity of symptoms of hypoglycemia (scores from 0 to 15)

SYMPTOMS	YES (1)	NO (0)	SCORE
Sweating			
Trembling			
Warmness			
Palpitations			
Tiredness			
Dizziness			
Confusion			
Lack of Concentration			
Light-Headedness			
Weakness			
Hunger			
Speech Disorder			
Double Images			
Nausea			
Paresthesias			
Total Score			

the previous neurophysiological tests. To obtain ERPs, the conventional technique with an acoustic ball paradigm was used [25]. Two types of tone, 2000Hz (target one) and 1000 Hz (target two), were delivered binaurally in random order at a rate of 0.5Hz and with a probability of 0.2 for the target tone through headphones at 40 dB normal hearing level (2ms rise/fall, 20ms plateau). After having the patients listen to the non-target and the target stimulation and acknowledge the difference between them, they were required to press a switch when noticing the infrequent target tones with their eyes open. Neural responses from the two types of stimuli were recorded separately at the Fz, Cz and Pz electrodes, (International 10–20 system) with the ear lobe and the forehead serving as the reference and the ground respectively. Electrode impedance was at 5kΩ and the filter band at 0.1–50 Hz. Trials with artifacts were excluded from the averages. The total number of stimuli was set at 30. Among neural response, recorded from the Cz electrode, the highest

Table II. Clinical profile and ancillary examinations of NIDDM patients and controls

	NIDDM Patients (N=44)	Controls (N=17)
Age (years) (Min–Max)	38–75	43–69
Mean±SD	58.84±8.4	56.53±8.09
Disease Duration (years) (Min–Max)	2–41	–
Mean±SD	10.52±7.97	
Gender (Male/Female)	12/32	2/15
Body Mass Index (Min–Max)	20–40	20–43.6
Mean±SD	28.66±4.18	28.35±5.98
Glucose (Min–Max)	81–354	73–103
Mean±SD	182.68±69.04	88.65±9.62
Glycosylated hemoglobin (Min–Max)	5.1–13.5	4.3–8.0
Mean±SD	8.28±2.09	5.74±0.95
Cholesterol (Min–Max)	107–334	144–306
Mean±SD	209.23±45.83	222.76±51.41
Triglycerides (Min–Max)	71–1206	86–617
Mean±SD	235.64±214.93	194.41±129.30
High Density Lipoprotein (Min–Max)	24–64	17–71
Mean±SD	38.5±9.04	41.71±13.45
Low Density Lipoprotein (Min–Max)	67–197	58–238
Mean±SD	130.15±32.74	141.31±50.97

Table III. ERP P300 measures in NIDDM patients according to the presence of retinopathy and to the number of episodes of hypoglycemia

Groups (Number)	ERP P300 values (Min–Max) Mean±SD	Statistical Analysis Test, significance
NIIDM Patients (N= 44)	296–450 366.59±35.63	Student's *t Test*, p<0.03*
Controls (n=17)	302–368 343.38±17.97	
NIDDM patients without retinopathy (N=36)	304–450 369.83±35.78	Student's *t Test*, p<0.20
NIDDM patients with retinopathy (N=8)	296–406 352.00±33.16	
NIDDM without hypoglycemic episodes (N=11)	314–418 359.64±30.92	ANOVA, F= 0.227, p<0.277
NIDDM < 5 hypoglycemic episodes (N=10)	296–450 371.40±46.46	
NIDDM >5 hypoglycemic episodes (N=9)	304–418 361.33±37.24	
NIDDM without hypoglycemic episodes (N=11)	314–418 359.64±30.92	Student's *t Test*, p<0.314
NIDDM with any hypoglycemic episodes (N=19)	296–450 366.63±41.50	

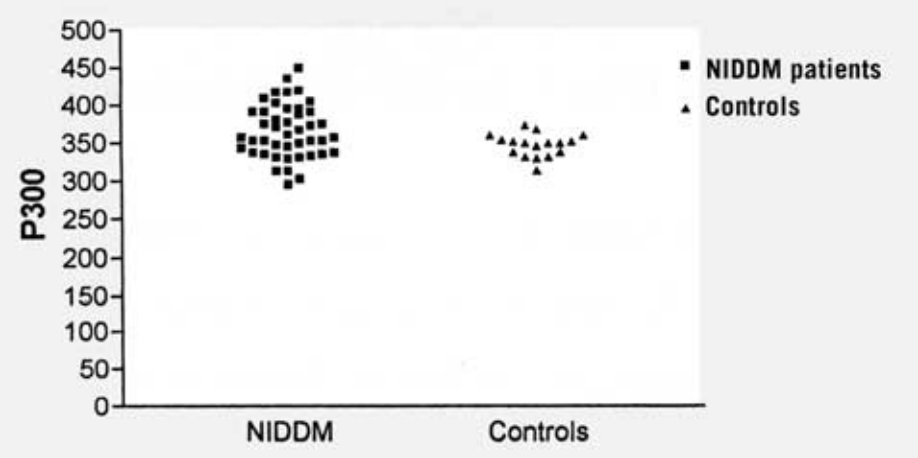

Figure 1. ERP P300 in NIDDM patients (n=44) was significantly different from controls (n=17) (Students t test, p<0,03).

positive peak between the potentials between 250 ms and 500ms was identified and its latency was measured as a neurophysiological parameter.
The local Ethics Committee approved the study.

Statistical analysis

Parametric data are expressed as mean (SD). ERP P300 measures and clinical and laboratory values were compared using a Pearson correlation test. To compare ERP P300 measures between groups, ANOVA followed by Bonferroni test or Students *t test* were used. Significance was established at $p<0.05$.

Results

A total of 44 patients were evaluated clinically and through the ERP P300 measure. Seventeen assymptomatic individuals without known pathology were matched by age and tested as controls. Table II expresses clinical characteristics and results of blood tests of NIDDM patients and controls. ERP P300 measures were related to age (Pearson, $p<0.001$) and not to disease duration, glucose levels, triglycerides or cholesterol.

Diabetic patients had significantly higher ERP P300 latency than controls (Student *t-test*, $p<0,03$) (Fig. 1). The presence of retinopathy did not influence ERP P300 latency (Table III). There was no difference in ERP P300 latency between groups of diabetic patients regarding the frequency or severity of previous hypoglycemic episodes (Table III). Patients without any history of previous hypoglycemic episodes showed a trend for lower values of the ERP P300 latency however, this difference was not significant (Table III).

Discussion

In this study, only individuals with good glucose control, normal cognitive function defined by a score greater than 26 with the MMSE and without other signs of NS involvement were included. NIDDM patients showed significantly higher latencies of ERP P300 than controls (Student's *t test*, $p<0.01$). P300 measures were related to age both in NIDDM patients and controls and age is probably the most important isolated factor influencing the ERP P300 latency.

The presence of retinopathy did not influence ERP P300 latency although other studies have indicated a trend for higher latencies in IDDM patients with retinopathy [8].

In NIDDM patients, improvement of P300 latency by treatment has been demonstrated [26]. Toxic effects of chronic hyperglycemia and the long-term benefits of near normalization of glucose levels in diabetes have been also well established [4,11,17]. Deleterious effects of hypoglycemia in the nervous system have been well documented [27,28]. Previously, studying IDDM patients, hypoglycemia did not influence ERP P300 latency [21] and this is in agreement with other studies that suggest that IDDM patients are more resistant to the deleterious effects of hypoglycemia in the brain [18,19,20]. Brain susceptibility to hypoglycemia may be influenced by previous exposure to hypoglycemia and chronic hypoglycemia may increase the threshold for brain detection of abnormal glucose levels [29,30,31,32]. It remains to be proved whether the hazards of undesired hypoglycemia will prevail over time in NIDDM patients making potential protective therapy decisive for the development of brain impairment [33]. Our evidence does not corroborate the chronic deleterious effects of accidental hypoglycemia in the nervous system, in agreement with other evidences from the literature reported from IDDM patients[19,21]. Hypoglycemia has undeniable potential lethal effects on the brain but the point is that chronic diabetic patients may develop a different metabolic approach. The increasing use of intensive insulin therapy will put forward this subject as a major issue for diabetic patients.

Controversy remains regarding the complex risk factors involved in the determination of brain damage in diabetes. Toxic metabolic substance as polyols, lactate, cerebral edema, ionic change or vascular pathology may play a more decisive role in chronic undetected brain damage in NIDDM patients.

REFERENCES

1 Pulsinelly WA, Levy DE, Sigsbee B, Scherer P, Plum F. Increased damaged after stroke in patients with hyperglycemia with or without established diabetes mellitus. Am J Med 1983; **74**:540–544.

2 Barzilay JI, Kronmal RA, Bittner V, Eaker E. Forster ED. Coronary artery disease in diabetic and nondiabetic patients with lower extremity arterial disease: A report from the Coronary Artery Surgery Study Registry. Am Heart J 1998; **135**:1055–1062.

3 Papademetriou V, Narayan P, Rubins H, Collins D, Robins S. Influence of risk factors on peripheral and cerebrovascular disease in men with coronary artery disease, low high-density lipoprotein cholesterol levels, and desirable low-density lipoprotein cholesterol levels. HIT Investigators. Department of Veterans affairs HDL Intervention Trial. Am Heart J 1998; **136**:734–740.

4 Diabetes Control and Complications Trial. Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; **329**:977–986.

5 Leland OS, Maki PC. Heart Disease and Diabetes Mellitus. In: Marble A, Krall AP, Bradley RF, Christlieb AR, Soeldnser JS, editors. Joslin's Diabetes Mellitus, 12th edition. Philadelphia: Lea & Febiger; 1985. p. 553–582.

6 Kugler CFA, Funk H, Vlajic P, Platt D. The relationship between endothelin-1, event related P300 potentials, and prognosis in cerebral arteriosclerosis. J Am Geriatr Soc 1997; **45**: 1228–1236.

7 Herold KC, Polonsky KS, Cohen RM, Levy J, Douglas F. Variable deterioration in cortical function during insulin-induced hypoglycemia. Diabetes 1985; **34**:677–685.

8 Kurita A, Katayama K, Mochio S. Neurophysiological evidence for highered brain functions in NIDDM. Diabetes Care 1996;**19**: 360–364.

9 Thomas M, Sherwin RS, Murphy J, Kerr D. Importance of cerebral blood flow to the recognition of and physiological responses to hypoglycemia. Diabetes 1997; **46**:829–33.

10 Tandon OP, Veram A, Ram BK. Cognitive dysfunction in NIDDM: P3 event related evoked potential study. Indian J Physiol Pharmacol 1999; **43**:383–388.

11 Dahl-Jorgensen K, Brinchman-Hansen O, Hanssen KF, Ganes T, Kierulf P, Smeland E, et al. Effect of near normoglycemia for two years on progression of early diabetic retinopathy, nefropathy and neuropathy: The Oslo Study. Br. Med J 1996; **293**: 1195–1199.

12 Bruno A, Biller J, Adams HP, Clarke WR, Woolson RF, Williams LS, et al. Acute blood glucose level and outcome from ischemic stroke. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. Neurology 1999; **52**:280–284.

13 Tallroth G, Lindgren M, Sternberg G, Rosen I, Agardh CD. Neurophysiological changes during insulin-induced hypoglycemia and in the recovery period following glucose infusion in type 1 (insulin-dependent) diabetes mellitus and in normal man. Diabetologia 1990; **33**:319–323.

14 Lindgren M, Eckert B, Stenberg G, Agardh CD. Restitution of neurophysiological functions, performance, and subjective symptoms after moderate insulin-induced hypoglycemia in non-diabetic men. Diabet Med 1996; **13**:218–225.

15 King P, Kong MF, Parkin H, MacDonald IA, Barber C, Tattersall RB. Intravenous lactate prevents cerebral dysfunction during hypoglycemia in insulin-dependent diabetes mellitus. Clin Sci 1998; **94**:157–63.

16 Defronzo RA, Hendler R, Christensen N. Stimulation of counter regulatory hormonal responses in diabetic men by a fall in glucose concentration. Diabetes 1980; **29**:125–131.

17 Gjedde A, Crone C. Blood-brain glucose transfer. Repression in chronic hyperglycemia. Science 1981; **214**:456–457.

18 Ziegler D. Effects of previous glycemic control on the onset and magnitude of cognitive dysfunction during hypoglycemia in type 1 (insulin-dependent) diabetic patients. Diabetologia 1992; **35**:828–834.

19 Jones TW, Borg WP, Borg MA, Boulware SD, MaCarthy G, Silver D, et al. Resistance to neuroglycopenia: an adaptive response during intensive insulin treatment of diabetes. J Clin Endocrinol Metab 1997; **82**:1713–1718.

20 Kramer L, Fasching P, Madl C, Schneider B, Damjancic P, Waldhausl W, et al.. Previous episodes of hypoglycemic coma are not associated with permanent cognitive brain dysfunction in IDDM patients on intensive insulin treatment. Diabetes 1998; **47**:1909–1914.

21 Blackman JD, Towle VR, Sturis J, Lewis GF, Spire JP, Polonsky KS. Hypoglycemic thresholds for cognitive dysfunction in IDDM. Diabetes 1992; **41**:392–329.

22 Pozzessere G, Elvira V, DeGrignis S, Cordischi VM, Fattaposta F, Rizzo PA, et al. Abnormalities of cognitive functions in IDDM revealed by ERP P300 event-related potential analysis. Diabetes 1991; **40**:952–958.

23 Uberall MA, Renner C, Edl S, Parzinger E, Wenzel D. VEP and ERP abnormalities in children and adolescents with prepubertal onset of insulin-dependent diabetes mellitus. Neuropediatrics 1996; **27**:88–93.

24 Dey J, Misra A, Deasi NG, Mahapatra Ak, Padma MV. Cognitive function in younger type II diabetes. Diabetes Care 1997; **20**:32–5.

25 Onofrj MC, Fulgente T, Nobilio D, Bazzano S, Colamartino P. Mapping of event-related potentials to auditory and visual oddball paradigms in controls. Eur Neurol 1991; **31**:220–228.

26 Mochizuki Y, Oishi M, Hayakawa Y, Matsuzaki M, Takasu T. Improvement of P300 latency by treatment in non-insulin-dependent diabetes mellitus. Clin Eletroencephalography 1998; **29**:194–196.

27 Lobmann R, Smid HGO, Pottag G, Wagner K, Heinze H-J, Lehnert H. Impairment and recovery of elementary cognitive function induced by hypoglycemia in type-1 diabetic patients and healthy controls. J Clin Endocrinol Metabol 2000; **85**: 2758–2766.

28 Ryan CM, Becker DJ. Hypoglycemia in children with type 1 diabetes mellitus. Risk factors, cognitive function and management. Endocrinol Metab Clin North Am 1999; **28**:883–900.

29 Simonson DC, Tamborlane WV, De Fronzo RA, Sherwin RS. Intensive insulin therapy reduces counter regulatory hormone responses to hypoglycemia in patients with type I diabetes. Ann Intern Med 1985; **103**:184.

30 Amiel SA, Tamborlane WV, De Fronzo RA, Sherwin RS. Defective glucose counterregulation after strict control of insulin-dependent diabetes mellitus. N Engl J Med 1985; **316**:1376–1383.

31 Mc Call AL, Fixman LB, Fleming N, Tornheim K, Chick W, Ruderman NB. Chronic hypoglycemia increases brain glucose transport Am J Physiol 1986; **251**:E442–E447.

32 Pelligrino DA, Segil LB, Albrecht RF. Brain glucose utilization and transport and cortical function in chronic vs. acute hypoglycemia. Am J Physiol 1990; **259**:E729–E735.

33 Papagapiou MP, Auer RN. Regional neuroprotective effects of the NMDA receptor antagonist MK-801 (dizocilpine) in hypoglycemic brain damage. J Cereb Blood Flow Metab 1990; **10**:270–276.