Journal of Neurological Sciences [Turkish] **28:(2)**# 27; 132-141, 2011
http://www.jns.dergisi.org/text.php3?id=425
Research Article

The Effect of Chronic N(G)-Nitro-L-arginine Methyl Ester (L-NAME) Administration on Visual Evoked Potentials and Oxidative Stress in Streptozotocin Induced Diabetic Rats

Yaşar Gül ÖZKAYA[1], Gülay HACIOĞLU[2], Vural KÜÇÜKATAY[3], Piraye YARGIÇOĞLU[4], Aysel AĞAR[2]

[1]Akdeniz Üniversitesi, Beden Eğitimi ve Spor Yüksekokulu, Antalya, Türkiye [2]Akdeniz Üniversitesi, Tıp Fakültesi Fizyoloji Anabilim Dalı, Antalya, Türkiye [3]Pamukkale Üniversitesi, Tıp Fakültesi Fizyoloji Anabilim Dalı, Denizli, Türkiye [4]Akdeniz Üniversitesi, Tıp Fakültesi Biyofizik Anabilim Dalı, Antalya, Türkiye

Summary

Objective: The aim of this study was to investigate the effects of N(G)-nitro-L-arginine-metyl-ester (L-NAME) on visual evoked potentials (VEPs) and oxidative stress in streptozotocin (STZ)–induced diabetic rats.
Methods: Wistar rats were assigned to one of four groups: control (C), diabetic (D), control + L-NAME (CN) and diabetic + L-NAME (DN). Diabetes was induced by a single intraperitoneal injection of STZ (60 mg/kg). Three days after the STZ injection, diabetes was confirmed by measuring tail blood glucose concentration. L-NAME was injected intraperitoneally to the CN and DN groups at a dose of 10 mg/kg/d for eight weeks. VEPs were recorded by a photic stimulator. Thiobarbituric acid-reactive substance (TBARS) as an index of oxidative stress, and nitrite levels were measured fluorometrically in the brain and retina tissues.
Results: L-NAME treatment produced a significant decrease in nitrite levels with respect to the control group, and body weight, water and food consumption and plasma glucose concentrations of the diabetic rats. TBARS concentrations were increased in diabetic rats. Although L-NAME treatment significantly increased the retina and brain TBARS levels in CN group, decreased TBARS concentrations were found in diabetic rats. All VEP components were significantly increased in diabetic rats. L-NAME caused a significant delay in all VEP components in CN group.
Conclusion: Our results clearly showed that although L-NAME improved clinical manifestations of diabetes such as polyphagia, polydipsia, and also plasma glucose and TBARS concentrations in brain and retina tissues, it did not alter prolonged VEP latencies in diabetic state.

Key words: Streptozocin diabetes, N(G)-Nitro-L-arginine Methyl Ester (L-NAME), evoked potentials, oxidative stress, rats

Kronik N(G)-Nitro-L-arginine Methyl Ester (L-NAME) Uygulamasının, Diabetic Sıçanlarda Görsel Uyarılmış Potansiyeller ve Oksidan Hasar Üzerine Etkisi

Özet

Amaç: Bu çalışmanın amacı, sıçanlarda oluşturulan streptozotosin diabet modelinde kronik L-NAME uygulamasının, görsel uyarılmış potansiyeller (GUP) ve oksidan hasar üzerine etkisini araştırmaktır.

Gereç ve Yöntem: Wistar sıçanlar 4 gruba ayrılmıştır: Kontrol (K), diabetik grup (D), L-NAME verilen grup (L) ve L-NAME verilen diabetik (DL) grup. Diabet, periton içine uygulanan tek doz (60 mg/kg) streptozotosin (STZ) ile oluşturulmuştur. STZ enjeksiyonundan 3 gün sonra, kuyruktan kan glukoz konsantrasyonu ölçülerek diyabet teyid edilmiştir. L-NAME, 8 hafta boyunca 10 mg/kg/gün periton içine uygulanmıştır. GUP, fotik stimülatör kullanılarak kaydedilmiştir. Beyin ve retina dokularında, oksidan hasar göstergesi olarak tiyobarbitürik asit reaktif ürünleri (TBARÜ), ve nitrit düzeyleri florometrik olarak ölçülmüştür.

Bulgular: L-NAME uygulaması, L ve DL grubunda beyin ve retina nitrit düzeylerini, diabetik grupta ise vücut ağırlığı, besin ve su tüketimi ve plazma glukoz konsantrasyonunu düşürmüştür. Diabetik gruplarda TBARÜ konsantrasyonları yüksek bulunmuştur. L grubunda L-NAME'in retina ve beyin TBARÜ düzeyini arttırdığı, buna karşılık diabetik grupta düşürdüğü saptanmıştır. Diabetik gruplarda tüm GUP latanslarında uzama saptanmıştır. L-NAME, L grubunda tüm GUP latanslarında uzamaya yol açmıştır.

Sonuç: Çalışmamızın sonuçları L-NAME uygulamasının, poliüri ve polifaji gibi diabete bağlı klinik bulguları, kan glukoz ve TBARÜ konsantrasyonunu azaltmasına karşılık, diabette ortaya çıkan GUP latanslarındaki uzamaya etkisiz olduğunu ortaya koymuştur.

Anahtar Kelimeler: Streptozotosin diabeti, N(G)-Nitro-L-arginine Methyl Ester (L-NAME), uyarılmış potansiyeller, oksidan hasar, sıçan

INTRODUCTION

Diabetes mellitus is a complex disease associated with hyperglycemia, which is thought to cause complications such as neuropathy and retinopathy[3]. Retinopathy, one of the characteristic retinal complications of hyperglycemia, is considered a significant cause of visual deficits in diabetes mellitus[4,9]. Although the pathogenesis of retinopathy is not clearly understood, a growing body of evidence suggests that reactive oxygen derivatives play an important role in damaging the retina in diabetes[2,19,25]. Accumulating evidence indicates that hyperglycemia stimulates numerous mechanisms that increase the production of oxidative nonenzymatic glycosylation[19,25].

Elevated nitric oxide (NO) production in the retina enhances lipid peroxidation in diabetes mellitus[39]. NO participates in excitatory amino acid- and free radical-mediated hyperglycemia and thus affects retinal metabolism[13]. NO interacts with the superoxide anion and thiol compounds, generating reactive nitrogen species (NOx), peroxynitrite (ONOO–) and S-nitroso thiols, including S-nitrosoglutathione. The lipid peroxidative effect of NO may be mediated via ONOO– , as it is a potent oxidant with a long half-life[32]. The brain is particularly sensitive to oxidative stress because of its high rate of oxygen consumption and the nonregenerative nature of neurons[23]. The retina receives a rich supply of oxygen and contains a large quantity of polyunsaturated fatty acids, especially in the photoreceptor layer[20,26]. Therefore, retinal tissue may be very susceptible to oxidative damage and subsequent lipid peroxidation. Thus, it is likely that the most severe consequences of lipid peroxidation occur in the visual system.

NO is involved in the processing of vision from the lowest level of retinal transduction to the control of neuronal excitability in the visual cortex[13]. Thus, diabetes-induced lipid peroxidation and NO synthesis causes dysfunction of the brain and retina[13,19], resulting in changes to the visual system. This study was undertaken to investigate the effect of diabetes on the visual system by assessing visual evoked potentials (VEPs), which consist of several components originating from the retina, optic pathway, subcortex and cortex. VEPs are sensitive and reliable indicators of changes in the visual system[8,15].

We measured diabetes mellitus-induced changes in VEPs and examined the effect of NO on these changes using the nitric oxide synthase (NOS) inhibitor, N(G)-nitro L-arginine methyl ester (L-NAME). In addition, we investigated the role of NO on lipid peroxidation and examined the effect of lipid peroxidation on the visual system. The levels of thiobarbituric-acid reactive substance (TBARS) were used as an indicator of lipid peroxidation. Nitrite levels in the retina and brain, which reflect the level of NO that is produced or released[36], were also measured.

MATERIAL AND METHODS

The Akdeniz University Animal Care and Use Committee approved the study protocol. Forty male Wistar rats aged 3 months were used in the study. Standard rat chow and tap water were offered ad libitum and the animals were housed in groups of four to five in stainless steel cages under standard environmental conditions (24 ± 2 ºC, 50 ± 5% relative humidity and a 12:12 h light : dark cycle). The animals were randomly allocated to one of four groups: control (C), control + L-NAME (CN), diabetic (D), diabetic + L-NAME (DN). After an overnight fast, diabetes was induced by a single intraperitoneal injection (60 mg/kg) of streptozotocin (S-0130, Sigma, St. Louis, MO, USA) in phosphate citrate buffer containing 2.30 g citrate monohydrate and 2.58 g dibasic anhydrous sodium phosphate per 200 mL deionised water (pH 4.5)[31]. The control group received an injection with an equivalent volume of citrate buffer. Three days after the streptozotocin injection, tail blood glucose concentrations were determined using Hypoguard Supreme petit strips and a glucometemer. On the day of the confirmation of diabetes, CN and DN groups started to receive daily intraperitoneal injections of L-NAME (10 mg/kg) for eight weeks when the respective solutions were administered to the control and diabetic groups. Body weight and daily food and water consumption were recorded. After eight weeks of treatment, VEPs were recorded and the animals were sacrificed by exsanguination.

Measurement of Visual Evoked Potentials (VEPs)

VEPs were recorded under ether anesthesia using stainless steel subdermal electrodes (Nihon Kohden NE 223 S, Nihon Kohden Corporation, Tokyo, Japan). The reference and active electrodes were placed 0.5 cm anterior and posterior to the bregma, respectively. An earth electrode was placed on the tail. After 5 min of dark adaptation, a photic stimulator (Nova-Strobe AB Biopac System, Santa Barbara, CA, USA) at the lowest intensity setting was used to provide a flash stimulus at a distance of 15 cm, which provided light over the entire pupil. The repetition rate of the flash stimulus was 1 Hz and the flash energy was 0.1 J. VEPs recordings were obtained from the right and left eyes, during which the eye not under investigation was covered with black carbon paper and cotton. Body C using a heating°temperature was maintained at 37.5–38.0 pad[16,29]. One hundred responses were averaged using Biopac MP100 data acquisition equipment (Biopac System).

Sample Collection

Animals were anesthetized with diethyl ether and their abdomens were opened using a midline incision. Blood samples were taken for analysis of plasma glucose concentration and the animals were sacrificed by cardiac puncture. The brain and retinas were then removed for analysis of levels of TBARS, nitrite and protein. The brains were washed in ice-cold physiological saline. Tissues for analysis of nitrite, TBARS and protein concentrations were placed in 2 mL of ice-cold 100 mmol/L potassium phosphate buffer (pH 7.5) containing 1 mmol/L ethylene diamine tetraacetic acid (EDTA). All tissue samples were rapidly sonicated using a thermally regulated sonicator (Bronson sonifier, 250) and were then centrifuged at 14,000 rpm in a micro centrifuge. The supernatant was used for determination of levels of TBARS, nitrite and protein.

Thiobarbituric Acid-Reactive Substance (TBARS) Assay

TBARS levels were measured using a fluorometric method and 1, 1, 3, 3-tetramethoxypropane as a standard[37]. Tissue samples (50 µL) were placed in tubes containing 1 mL distilled water. After addition of 1 mL of a solution containing 29 mmol/L 2-thiobarbituric acid in acetic acid (8.75 mol/L), samples were placed in a water bath and heated for 1 h at 95–100 ºC. After the samples had cooled, 25 µL of 5 mol/L HCl was added and the reaction mixture was extracted by agitation for 5 min with 3.5 mL of n-butanol. After centrifugation, the butanol phase was separated and the fluorescence of the butanol extract was measured using a spectrofluorometer (Shimadzu RF-500; Shimadzu Kyoto, Japan) set at wavelengths of 525 nm for excitation and 547 nm for emission.

Nitrite Assay

Nitrite levels were measured using the fluorometric method of Ohta et al.[27]. Brain and retina sonicates (1.5 mL) were centrifuged at 14,000 rpm for 10 min at 4 ºC, after which 1 mL of the supernatant was used for nitrite analysis. The aliquots were added to 0.5 mL of 0.04% (wt/vol) 4 hydroxycoumarin in 1:1 (vol/vol) dimethylformamide: 2N HCl and incubated for 5 min at 0 ºC. Then, 50 µL of 8% (wt/vol) sodium thiosulfate was added, followed by a 5 min incubation at room temperature. Next, 0.5 mL of 1.5 mol/L NaOH was added and fluorescence was determined at room temperature using a spectrofluorometer (Shimadzu RF-500) equipped with a 347 nm excitation filter and a 453 nm emission filter. Relative fluorescence was measured relative to a 1.0 mL aliquot of sonication buffer and calibrated using internal and external nitrite standards. Nitrite levels are expressed as picomoles per milligram soluble protein. Protein levels were determined using Lowry's method[24].

Statistical Analysis

Data are expressed as the mean ± S.E. The statistical significance of differences between means was assessed using analysis of variance followed by Tukey's HSD post hoc test. A probability level of < 0.05 was considered significant.

RESULTS

The mean initial and final body weights and daily food intakes for the six treatment groups are shown in Table 1. The final daily food and water intakes of the diabetic groups were significantly greater than the respective final intakes than that of the control group. As expected, the final body weights of the diabetic groups were lower than their respective pretreatment body weights and that of the control group. L-NAME resulted in a marked reduction in the final body weight, water and food consumption of the diabetic rats.

Plasma glucose concentrations in the diabetic groups were significantly elevated compared with that of the control group (Table 2) and the diabetic groups exhibited

polydipsia and polyphagia (Table 1). Although L-NAME administration to the diabetic rats decreased glucose levels compared with that of the diabetic group (group D), the glucose levels of DN group were greater than that of the control group (group C).

Brain and retinal TBARS and nitrite levels are shown in Table 3. Brain and retina TBARS concentrations were significantly higher in CN and D groups than in control rats. L-NAME exposure caused a decrement on brain and retina TBARS levels in diabetic rats compared with the C group. Brain and retinal nitrite levels were significantly elevated in the diabetic group compared with the control group, but found to be decreased in diabetic L-NAME group than in the diabetic and control rats.

Differences between visual evoked potential (VEP) parameters were analyzed by using ANOVA and Tukey's highest significant difference test. No significant difference was observed in VEP latencies and amplitudes between right and left eyes. Therefore, based on the analysis, the data from stimulation of both eyes were averaged. The means and standard deviations of peak latencies and peak-to-peak amplitudes of VEP components and the results of statistical analysis are shown in Tables 4 and 5. The mean latencies of the P_1, N_1, P_2, N_2 and P_3 components were significantly prolonged in the CN and diabetic groups compared with the control group. Although L-NAME did not affect P_1, P_2, N_2 and P_3 latencies in the DN group compared with the D group, increased N_1 latency was found in the DN group compared with the C and D groups.

Diabetes mellitus and L-NAME had no effect on the amplitude of VEP components compared with the respective control groups.

Table1: Initial and final body weights and daily food and water consumption.

	Initial weight (g)	Final weight (g)	Initial water consumption (mL/100 g body weight)	Final water consumption (mL/100 g body weight)	Initial food consumption (g/100 g body weight)	Final food consumption (g/100 g body weight)
C	249.18± 4.82	360,20± 11,00	8.99±0.55	9,24±0,52	5.610±1.46	4,92±0,21
CN	246.83±5.78	302,120±5,98*,#	9.09±0.78	8,76±0,93	5.55±0.38	5,51±0,32#
D	245.27±6.02	229,10± 8,23*	9.17±0.63	48,22±2,09*	5.71±0.16	16,44±0,59*
DN	239.66±5.94	199,13±8,14*,**	8.49±1.00	30,74±3,26*,#,**	5.70±1.58	12,65±0,99*,#,**

Each value represents the mean ± S.E. (n = 10). Drugs were administered intraperitoneally. C; control, CN; control + L-NAME, D; diabetic and DN; diabetic + L-NAME groups. * Significantly different from the control group, # Significantly different from the diabetes group, ** Significantly different from the CN group.

Table 2: Plasma glucose concentrations of the control and diabetic groups (mg/dL).

C	CN	D	DN
112,20±5,52	99,80±4,56	402,91 ± 17,62 *	280,63±16,10 *#,**

Each value represents the mean ± S.E. (n = 10). Drugs were administered intraperitoneally. C; control, CN; control + L-NAME, D; diabetic and DN; diabetic + L-NAME groups. * Significantly different from the control group. # Significantly different from the diabetes group, ** Significantly different from the CN group.

Table 3: Brain and retina TBARS and nitrite levels of the control and diabetic groups (nmol per g protein).

	Brain TBARS	Retinal TBARS	Brain nitrite	Retinal nitrite
C	1,89 ± 0,07	2.31 ± 0.11	0,89 ± 0,01	1.66 ± 0.08
CN	3,46 ± 0,08* #	3.89 ± 0.0 9*,#	0,94 ± 0,05#	1.14 ± 0.03*,#
D	2,89 ± 0,28*	3.41 ± 0.15 *	1,64 ± 0,06*	2.07 ± 0.08*
DN	2,61 ± 0,06*,**	1.68 ± 0.12 *,#,**	0,61 ± 0,06*,#,**	1.12 ± 0.14*,#

Each value represents the mean ± S.E. (n = 10). Drugs were administered intraperitoneally. C; control, CN; control + L-NAME, D; diabetic and DN; diabetic + L-NAME groups. TBARS: Thiobarbituric-acid reactive substances. * Significantly different from the control group. # Significantly different from the diabetes group. ** Significantly different from the CN group.

Table 4: Means and standard errors of peak latencies for each VEP component (ms).

	P_1	N_1	P_2	N_2	P_3
C	18.05 ± 0.44	31.40 ± 0.85	46.10 ± 1.49	65.70 ± 1.35	91.60 ± 1.29
CN	26.80 ± 1.21 *	42.95 ± 1.61 *,#	63.60 ± 2.19 *	82.50 ± 2.32 *	120.90 ± 2.17 *
D	28.85 ± 0.84 *	48.85 ± 1.14 *	67.20 ± 2.16 *	88.60 ± 1.80 *	122.50 ± 1.83 *
DN	32.50 ± 1.55 *	54.20 ± 1.69 *,#	70.60 ± 1.86 *	87.60 ± 2.76 *	122.90 ± 3.68 *

Each value represents the mean ± S.E. (n = 10). Drugs were administered intraperitoneally. C; control, CN; control + L-NAME, D; diabetic and DN; diabetic + L-NAME groups. VEP: visual evoked potential. * Significantly different from the control group. # Significantly different from the diabetes group.

DISCUSSION

The STZ-diabetic rat is a well-characterized animal model of type I diabetes mellitus for metabolic studies[5,38]. In streptozotocin–induced diabetes, hyperglycemia is caused by damage to pancreatic beta cells. In our study, diabetic rats were characterized by marked body weight loss and elevated food and water intake. Plasma glucose concentration was 3.5-fold higher in the diabetic groups compared with the control group, indicating that hyperglycemia was sustained in the diabetic rats. These results are in accordance with the results of previously reported after treatment of streptozotocin-diabetic rats[31]. The effectiveness of L-NAME treatment in this animal model has been demonstrated previously[7], and it was confirmed in the present study, since there was a significant reduction in food and water consumption and plasma glucose levels in diabetic rats that received treatment with L-NAME. Once the food and water intake of the DN group was increased compared to the D group, their energy expenditure and body fat utilization might be increased due to L-NAME administration, and the final result was a reduction of body weight in these animals. A previous study by Seven et al. has been shown that L-NAME administration suppresses streptozotocin-induced diabetes in rats by inhibiting oxidative stress[34], in our study the plasma glucose concentration of the DN group was higher than that of the control group.

The present study was undertaken to investigate the effect of L-NAME on the visual system by assessing VEPs. Although it is known that changes in neurotransmitters affect the latencies of VEP, there is a lack of information on the effects of NO, an accepted neurotransmitter, on VEPs[10]. It is well known that VEPs are sensitive indices of early alterations in optic pathways in some clinical entities and that they are useful for evaluating visual function[22,30]. The generators of the P1 peak have not been determined, but it has been suggested that this component corresponds to the upper nasal portions of the visual field in areas 17 and 18a[12]. The P2 components of VEP are believed to reflect the cortical response to the initial afferent volley from the retina through the lateral geniculate nucleus[21,33]. Thus, changes in this portion of the VEP waveform are indicative of altered function in the "front end" of the visual system. However, N2 represents the initial excitatory response in the middle laminae to the visual stimulus, and the subsequent positive peak, P3, is reported to reflect the excitatory postsynaptic response of pyramidal cells in the upper laminae[11]. The P2 and N2 peaks may represent hyperpolarization and depolarization, respectively, of stellate cells in lamina IV[11,21]. In our study, diabetes was associated with significant latency prolongations of all VEP components, which is consistent with many reports in the literature[1,30]. Early alterations in VEPs were first observed in the optic pathways of diabetic patients[35]. In our study, latencies of VEP components were prolonged by L-NAME both in CN and DN groups with respect to the control group. Thus, our results indicate that the latencies of VEPs are delayed by inhibition of NOS in control animals, whereas L-NAME has no additive effect on any of the components of VEP in diabetic state.

The present study also showed that diabetes mellitus caused an increase in the lipid peroxidation process and this was accompanied by changes in VEPs. Furthermore, L-NAME produced a significant increase in TBARS levels and VEP latencies in CN group. Although L-NAME caused a significant decrement in brain and retina TBARS concentrations, unaltered VEP latencies were found in the DN group with respect to the D group. It is noteworthy that, L-NAME treatment resulted decreased concentrations of retina

TBARS with respect to the control animals in DN group. This finding suggests that retina has greater sensitivity on L-NAME-induced lipid peroxidation than the brain tissue.

NO is known the main gaseous signaling molecule in the visual system. Both constitutive formation of NO and inducible expression of iNOS have been reported to occur in the brain and retina during diabetes. In the present study, opposing findings of L-NAME administration on TBARS and VEPs in control and diabetic rats, may be explained by the paradoxical effect of NO under different conditions. While under normal conditions NO plays a physiological role as a neurotransmitter in the central nervous system, but excessive release of NO may be toxic to cells. First, previous studies suggested that the NO synthesized by eNOS is physiological but NO synthesized by iNOS and nNOS is pathologic[13]. Second, the paradoxical effect of NO has been explained by its redox state. Under physiological conditions, NO is found in the forms of nitrogen monoxide (NO.) and nitrozonium cation (NO^+). If the redox state of tissue is convenient for the formation of NO., a neurotoxic effect is seen. However, if the environment is convenient for the formation of NO^+, it suppresses the activity of NMDA receptors and shows a neuroprotective effect[14,28]. Third, some results suggest that the lipid peroxidative effect of NO is seen in pathological conditions. Thus, the radical or antioxidant-like behaviour of NO varies according to whether the superoxide concentration is high or low. In the former case, NO leads to lipid peroxidation, whereas in the latter case, NO acts as an antioxidant. This behaviour is said to be dependent on the rate of NO and O_2-. If that rate is smaller than one, NO becomes an oxidant, but if the rate exceeds one NO becomes an antioxidant[10,18]. In conclusion, parallel to previous studies, the present study provides evidence of both radical and antioxidant effects of NO in control and streptozotocin-induced diabetic rats.

VEP-changing effect of diabetes mellitus could also be caused by other mechanisms associated with alterations in the electroconductive properties of the myelin sheath such as metabolic disturbances and impaired incorporation of acetate and glucose into nerve lipids[6,17].

Our results can be summarized as follows:

1. Although L-NAME did not affect metabolic parameters in control animals, improved plasma glucose concentrations were found in DN group.

2. Latency prolongations in VEPs after L-NAME administration may at least be partially implicated in the enhancement of lipid peroxidation in control animals.

3. Streptozotocin-induced diabetes caused a significant enhancement of lipid peroxidation in the brain and retina, and prolonged VEP latencies, and that these alterations did not improved by L-NAME administration.

In conclusion, our results show that although L-NAME administration resulted improved plasma glucose and brain and retina TBARS concentrations, the latencies of all VEP components are prolonged in diabetes and that L-NAME has no restorative effect on any of the components of VEP in diabetic rats. Further studies may provide more details that could help in solving the mechanism of visual system impairment in diabetes mellitus.

Acknowledgement

This study was supported by a grant from Akdeniz University Research Fund (98.01.0103.06). We all thank to Erol Nizamoğlu for technical assistance.

Correspondence to:
Yaşar Gül Özkaya
E-mail: gulozk@yahoo.com

Received by: 19 October 2010
Accepted: 13 February 2011

The Online Journal of Neurological Sciences (Turkish) 1984-2011
This e-journal is run by Ege University Faculty of Medicine,
Dept. of Neurological Surgery, Bornova, Izmir-35100TR
as part of the Ege Neurological Surgery World Wide Web service.
Comments and feedback:
E-mail: editor@jns.dergisi.org
URL: http://www.jns.dergisi.org
Journal of Neurological Sciences (Turkish)
Abbr: J. Neurol. Sci.[Turk]
ISSNe 1302-1664

REFERENCES

1. *Agar A, Kucukatay V, Yargicoglu P et al. The effect of sulfur dioxide inhalation on visual evoked potentials, antioxidant status and lipid peroxidation in alloxane-induced diabetic rats. Arch Environ Contam Toxicol 2000;39:257-264.*
2. *Ali TK, El-Remessy AB. Diabetic retinopathy: current management and experimental therapeutic targets. Pharmacotherapy 2009;29:182-92.*
3. *Bloomgarden ZT. Diabetic retinopathy and diabetic neuropathy. Diabetes Care 2007;30:760-765.*
4. *Bloomgarden ZT. Diabetic retinopathy. Diabetes Care 2008;3:1080-1083.*
5. *Brosnan JT, Man KC, Hall DE, Colbourne SA, Brosnan ME. Interorgan metabolism of amino acids in streptozotocin-diabetic ketoacidotic rat. Am J Physiol Endocrinol Metab 1983;244:E151–E158.*
6. *Buller N, Laurian N, Shvili I, Laurian L. Delayed brainstem auditory evoked responses in experimental diabetes mellitus. J Laryngol Otol 1986;100:883-891.*
7. *Catanzaro OL, Marina-Prendes MG, Hope SI, Zuccollo A, Dominguez A. Streptozotocin-induced hyperglycemia is decreased by nitric oxide inhibition. Braz J Med Biol Res 1994;27:2043-7.*
8. *Celesia GG. Evoked potentials techniques in evaluation of visual function. J Clin Neurophysiol 1984;1:55-76.*
9. *Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet 2010; 376:124–36.*
10. *Cudeiro J, Rivadulla C. Sight and insight-on the physiological role of nitric oxide in the visual system. Trends Neurosci 1999;22:109–116.*
11. *Du Y, Sarthy VP, Kern TS. Interaction between NO and COX pathways in retinal cells exposed to elevated glucose and retina of diabetic rats. Am J Physiol 2004;287:R735-741.*
12. *Espinoza HC, Thomas SG. Retinotopic organization of striate and extrastriate visual cortex in the hooded rat. Brain Res 1983;272:137-144.*
13. *Giove TJ, Deshpande MM, Gagen CS, Eldred WD. Increased neuronal nitric oxide synthase activity in retinal neurons in early diabetic retinopathy. Mol Vis 2009;15:2249-58.*
14. *Goldstein IM, Ostwald P, Roth S. Nitric oxide: a review of its role in retinal function and disease. Vision Res 1996; 36:2979–2994.*
15. *Halliday AM. Visual evoked responses in optic nerve disease. Trans Ophtalmol Soc UK 1976;96:372-376.*
16. *Hetzler BE, Boyes WK, Creason J, Dyer RS. Temperature dependent changes in visual evoked potentials of rats. Electroenceph Clin Neurophysiol 1988;70:137-154.*
17. *Kakkar R, Kalra J, Mantha SV, Prasad K. Lipid peroxidation and activity of antioxidant enzymes in diabetic rats. Mol Cell Biochem 1995;15:113-119.*
18. *Kashii S, Mandai M, Kikuchi M et al. Dual actions of nitric oxide in N-methyl-d-aspartate reseptor-mediated neurotoxicity in cultured retinal neurons. Brain Res 1996;711:93–101.*
19. *Kowluru RA, Chan PS. Oxidative stress and diabetic retinopathy. Exp Diabetes Res 2007;2007:43603.*
20. *Kowluru RA, Engerman RL, Kern TS. Abnormalities of retinal metabolism in diabetes or experimental galactosemia VIII. Prevention by aminoguanidine. Curr Eye Res 2000;21:814-819.*
21. *Kraut MA, Arezzo JC, Vaughan HGJ. Intracortical generators of the flash VEP in monkeys. Electroenceph Clin Neurophysiol 1985;62:300-312.*
22. *Kucukatay V, Hacioglu G, Savcioglu F, Yargicoglu P, Agar A. Visual evoked potentials in normal and sulfite oxidase deficient rats exposed to ingested sulfite. Neurotoxicol 2006;27;1:93-100.*
23. *Kumar JS, Menon UP. Effects of diabetes on levels of lipid peroxides and glycolipids in rat brain. Metabolism 1993;42:1435-1439.*
24. *Lowry OH, Rosenbrough NJ, Far AL, Randel RJ. Protein measurement with folin-phenol reagent. J Biol Chem 1951;193: 265-275.*
25. *Madsen-Bouterse SA, Kowluru RA. Oxidative stress and diabetic retinopathy: Pathophysiological mechanisms and treatment perspectives. Rev Endocr Metab Disord 2008;9:315–327.*
26. *Matsumoto S, Koshiishi I, Inoguchi T, Nawata H, Utsumi H. Confirmation of superoxide generation via xanthine oxidase in streptozotocin-induced diabetic mice. Free Radic Res 2003;37:767-72.*
27. *Ohta T, Arai Y, Takitani S. Fluorometric determination of nitrite with 4-hydroxycoumarin. Anal Chem 1986;58:3132-3135.*
28. *Oku H, Yamaguchi H, Sugiyama T, Kojima S, Ota M, Azuma I. Retinal toxicity of nitric oxide released by administration of a nitric oxide donor in the albino rabbit. Invest Ophthalmol Vis Sci 1997;38:2540–2544.*
29. *Ozkaya YG, Agar A, Hacioglu G, Yargicoglu P, Abidin I, Senturk UK. Training induced alterations of visual evoked potentials are not related to body temperature. Int J Sports Med 2003; 24:359-62.*
30. *Ozkaya YG, Agar A, Hacioglu G, Yargicoglu P. Exercise improves visual deficits tested by visual evoked potentials in streptozotocin-induced diabetic rats. Tohoku J Exp Med 2007; 213;4:313-21.*

31. *Ozkaya YG, Agar A, Yargicoglu P, Hacioglu G, Bilmen-Sarikcioglu S, Ozen I, Aliciguzel Y. The effect of exercise on brain antioxidant status of diabetic rats. Diabetes Metab 2004; 28:377–384.*
32. *Rubro H, Radi R, Anselmi D. Nitric oxide reaction with peroxyl radicals spares alpha- tocopherol during lipid peroxidation. Greater oxidant protection from the pair nitric oxide /alpha-tocopherol/ascorbate. J Biol Chem 2000;275:10812-10818.*
33. *Schroeder CE, Tenke CE, Givre, SJ, Arezzo JC, Vaughan HGJ. Striate cortical contribution to the surface-recorded pattern-reversal VEP in alert monkey. Vision Res 1991;3:1143-1157.*
34. *Seven A, Güzel S, Seymen O, Civelek S, Bolayırlı M, Yiğit G and Burçak G. Nitric oxide synthase inhibition by L-NAME in streptozotocin induced diabetic rats: impacts on oxidative stress. Tohoku J Exp Med 2003;199:205-210.*
35. *Sobrevia, L, GE Mann GE. Dysfunction of the endothelial nitric oxide signalling pathway in diabetes and hyperglycaemia. Exp Physiol 1997; 82: 423.*
36. *Suzuki Y, Ikari H, Hayashi T, Iguchi A. Central administration of a nitric oxide synthase inhibitor impairs spatial memory in spontaneous hypertensive rats. Neurosci Lett 1996;207:105-108.*
37. *Wasowicz W, Jean N, Peratz A. Optimized steps in fluorometric determination of thiobarbituric acid-reactive substances in serum. Importance of extraction pH and influence of sample preservation and storage. Clin Chem 1993;39:2522-2526.*
38. *Wu G, Meininger CJ.Impaired arginine metabolism and nitric oxide synthesis in coronary endothelial cells of the spontaneously diabetic BB rat. Am J Physiol Heart Circ Physiol 1995;269:1312–1318.*
39. *Zheng L, Kern TS. Role of nitric oxide, superoxide, peroxynitrite and PARP in diabetic retinopathy. Front Biosci 2009;14:3974-87.*