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Exercise Improves Visual Deficits Tested by Visual Evoked Potentials in Streptozotocin-Induced Diabetic Rats

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Özkaya, Y.G., Ağar, A., Hacioğlu, G. and Yargiçoğlu, P. *Exercise Improves Visual Deficits Tested by Visual Evoked Potentials in Streptozotocin-Induced Diabetic Rats*. Tohoku J. Exp. Med., 2007, **213** (4), 313-321 —— Visual evoked potentials (VEP) can be used as an objective non-invasive method to study the electrical activity of the visual system. Latency and amplitude measurements of VEP demonstrated that diabetes mellitus has been associated with increases in the latencies whereas the amplitude measurements revealed contradictory results. Although physical exercise has been reported to reduce the complications of diabetes mellitus, the effect of exercise on the visual system remains unknown. We investigated the effects of long-term moderate physical exercise on VEP in streptozotocin (STZ)-diabetic rats. We also measured brain thiobarbituric acid-reactive substances (TBARS) to explore the possible contribution of lipid peroxidation on the visual system. Animals were divided into four groups: control (C), control exercise (CE), diabetic (D) and diabetic exercise (DE) groups. Diabetes was induced by a single intraperitoneal injection of STZ (60 mg/kg). Three days after the confirmation of diabetes, DE and CE groups were trained by running on a motor-driven treadmill with a progressive eight-week programme. The animals began running at 10 m/min, 0° slope, 10 min/day and reached a level of 28 m/min, 6° slope, 60 min/day by week 8. TBARS were elevated and VEP latencies were delayed in diabetic rats, indicating diabetes-induced defects in the optic pathway. These prolonged latencies were restored by exercise training. VEP amplitudes of the DE group were found unaltered with the exception of a decrement in P_2N_2 which represents an early component of VEP, suggesting that exercise improves visual system defects in diabetic animals at different levels of the optic pathway. ——
diabetes mellitus; visual evoked potentials; exercise; lipid peroxidation; rat
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Physical exercise is well known to have many beneficial effects on human health. Recently, attention has largely focused on the increase of free radicals generated during exercise, especially during aerobic activities. This increase is related to the elevation of electron transport flux, mitochondrial oxygen consumption, energy demand, oxygen supply and body

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temperature (Sen 1995; Dekkers et al. 1996; Hoffman et al. 2007).

In the last decade, it has become widely accepted that increased free radical generation plays an important role in the pathogenesis of various disease states, such as diabetes mellitus, atherosclerosis and Parkinson's disease (Yan et al. 1994; Lawler and Powers 1998; Betteridge 2000). Diabetes mellitus is a complex disease associated with hyperglycaemia, which is thought to cause the development of diabetic complications such as neuropathy, nephropathy, retinopathy (Boynes 1991; Biessels et al. 1999; Bloomgarden 1999) and cardiovascular disease (Fujiwara et al. 2005; Sargin et al. 2005).

Accumulating evidence suggests that reactive oxygen-derived radicals play a crucial role in the development of diabetic retinopathy (Boynes 1991; Giugliano et al. 1996; Hartnett et al. 2000; Kowluru and Chan 2007). Mechanisms that contribute to increased oxidative stress in diabetes may include increased non-enzymatic glycosylation, autooxidative glycosylation, metabolic stress and alterations in sorbitol pathway activity (Vlassara 1997; Chen et al. 2006). On the other hand, the brain is particularly sensitive to the oxidative stress due to its high rate of oxygen consumption. In addition, the presence of high levels of unsaturated fatty acids, which are targets of the free radicals in the brain, make this organ susceptible to oxidative damage (Kumar and Menon 1993).

Physical exercise has been suggested to be beneficial in the management of diabetes mellitus (Gruber et al. 2006; Warburton et al. 2006; Constans and Lecomte 2007). However, the relationship between exercise and the oxidative status of the brain in diabetes mellitus has not been fully elucidated. Therefore, the main goal of our research was to clarify this point and to establish whether exercise can be recommended in diabetic alterations of the brain lipid peroxidation.

Visual evoked potentials (VEP) have been shown to be a sensitive method for detecting the involvement of optic pathways in various ophthalmological disorders, demyelinating diseases, optic neuritis and ischemic optic neuropathy, which are not always detectable by routine ophthalmological examination (Dorfman 1983; Anastasi et al. 1985; Yaltkaya et al. 1988).

Previous studies have revealed shortened VEP latencies in trained subjects compared to sedentary subjects (Ozkaya et al. 2003; Ozmerdivenli et al. 2005). Delpont et al. (1997) found shortened patterned reversal visual evoked potential (PREP) latencies in a group of tennis players but found that they were unaltered in rowers compared to control subjects. Some factors for exercise-induced changes in VEP latencies may be the elevation of catecholamine and dopamine in the brain and changes in body temperature. It is possible that elevated free radicals may trigger a lipid peroxidation reaction in the brain and retina (Hatfield and Landers 1987).

Therefore, we examined the alterations in latencies and amplitudes of VEP related to diabetes and training groups. Additionally, we decided to study the effects of exercise on diabetic rats in an attempt to understand the role of free radicals in the mechanisms of diabetes and exercise. In this context, thiobarbituric acid-reactive substances (TBARS) were determined as an indicator of lipid peroxidation during exercise and diabetic conditions.

Material and Methods

Animal care and exercise training

The study protocol was approved by the Akdeniz University Animal Care and Use Committee. Forty male Wistar rats (aged three months) bred in our laboratory were used in this study. Standard rat chow and tap water were given ad libitum and the animals were housed in groups of 4-5 rats in stainless steel cages at standard conditions (24 ± 2°C and 50 ± 5% humidity) with 12 : 12 hrs' light-dark cycles. Animals were randomly divided into four groups: Control (C), diabetic (D), control exercise (CE) and diabetic exercise (DE). Following an overnight fast, diabetes was induced by a single intraperitoneal injection (60 mg/kg) of streptozotocin (S-0130: Sigma, St. Louis, MO, USA) in a citrate buffer. The buffer was citrate phosphate: 2.30 g citrate monohydrate, 2.58 g sodium phosphate dibasic anhydrous in 200 ml deionized water (pH: 4.5) (Mitton et al. 1993). The other two groups were injected with an equivalent volume of citrate buffer. Three days later, the glucose concentration in the

tail blood of streptozotocin-administered rats was determined with Hypoguard Supreme Petit strips with a glucometer.

The rats were weighed weekly and daily food and water consumption were recorded during the experiments. The mean daily food and water consumption was estimated from the recorded values. At the end of the 8th week of the experimental period, rats were deprived of food for 24 hrs and prepared for the experimental procedure under ether anaesthesia.

One streptozotocin-treated group and one control group were trained by running on a motor-driven treadmill five days per week. Familiarization of the rats with the treadmill began two days before the injection of streptozotocin or vehicle. Running time and speed were gradually increased during the eight weeks of training. The animals began running at 10 m/min, 0% slope, 10 min/day and reached a level of 28 m/min, 6% slope, 60 min/day by the 8th week (Kainulainen et al. 1994). Because rats are nocturnal mammals, exercise training was performed in the dark cycle of the animals. Shortly after the run (5 min), blood samples were taken into a capillary tube from the tail vein to measure lactate levels. The blood lactate measurement was made to determine the anaerobic threshold of rats and was performed by using commercial kits (Abott aeroset, 73052HW00, Abott Labs, Abott Park, IL, USA).

VEP recordings

Visual evoked potentials were recorded with stainless steel subdermal electrodes (NE 223 S: Nihon Kohden, Tokyo). The reference and active electrodes were placed 0.5 cm in front of and behind the bregma, respectively. A ground electrode was placed on the tails of the animals. After 5 min of dark adaptation, a photic stimulator (Nova-Strobe AB) at the lowest intensity setting was used to provide a flash stimulus at a distance of 15 cm, which allowed lighting of the entire pupilla from the temporal visual field. The repetition rate of flash stimuli was 1 Hz and the flash energy was 0.1 J. VEP recordings from both right and left eyes were obtained, and throughout the experiments the eye not under investigation was occluded by black carbon paper and cotton. Body temperature was maintained between 37.5 and 38ºC by a heating pad (Hetzler et al. 1988).

The averaging of 100 responses was accomplished with an average of Biopac MP100 data acquisition equipment. Analysis time was 300 msec. The frequency bandwidth of the amplifier was 1-100 Hz. The gain was selected as 5,000 μV/div. The microprocessor was programmed to reject any sweeps contaminated with larger artifacts, and at least two averages were obtained to ensure response reproducibility. Peak latencies of the components were measured from the stimulus artifact to the peak in msec. Amplitudes were measured as the voltage between successive peaks.

Sample collection

Three days after the last bout of exercise, animals were anaesthetized with diethyl ether and their abdomens were opened by a midline incision. Blood samples were taken to determine the glucose level and animals were killed by cardiac puncture. The brain was then removed. Brain tissue homogenates were used for TBARS analysis.

TBARS assay

TBARS levels were measured by a fluorometric method developed by Wasowicz et al. (1993) using 1, 1, 3, 3-tetramethoxypropane as a standard, and the results are given as nmol/mg protein. Tissue samples (50 μl) were introduced to a tube containing 1 ml of distilled water. After the addition of 1 ml of a solution containing 29 mmol/l 2-thiobarbituric acid (TBA) in acetic acid (8.75 mol/l), samples were placed in a water bath and heated for 1 hr at 95-100°C. After the samples had cooled, 25 μl of 5 mol/l HCl were added and the reaction mixture was extracted by agitation for 5 min with 3.5 ml of n-butanol. After centrifugation, the butanol phase separated and the fluorescence of the butanol extract was measured in a spectrofluorometer (Shimadzu RF-5000, Kyoto) using wavelengths of 525 nm, for excitation, and 547 nm, for emission. The results were given as nmol/g protein. Protein content was determined by the method of Lowry et al. (1951) using bovine serum albumin as the standard.

Statistical analysis

Data are expressed as means ± S.E., and the statistical significance of the data was assessed by analysis of variance followed by Tukey's post hoc test. A level of $p < 0.05$ was accepted as statistically significant.

Results

Body weight and food intake

The mean body weight and daily food and water intakes of rats of the four groups are shown in Table 1. Exercise trained animals did not exhibit a marked change in either food or water

TABLE 1. Initial and final body weight and daily consumption of food and water of the four groups of rats. Values are means ± S.E.

Group	Body weight (g)		Daily consumption			
	Initial	Final	Food (g)		Water (ml)	
			Initial	Final	Initial	Final
Control	247.30 ± 5.20	346.80 ± 9.82††	5.54 ± 0.12	7.01 ± 0.20††	6.28 ± 0.14	9.25 ± 0.26††
Control exercise	241.30 ± 5.24	314.00 ± 6.23††	5.61 ± 0.09	6.39 ± 0.12††	5.85 ± 0.08	6.07 ± 0.12*
Diabetic	246.70 ± 4.85	233.60 ± 9.18**,†	5.59 ± 0.08	16.22 ± 0.63**,†	5.88 ± 0.08	20.44 ± 0.78**,†,††
Diabetic-exercise	240.30 ± 4.10	246.50 ± 9.63**,†	5.54 ± 0.11	14.57 ± 0.57**,†	5.97 ± 0.16	19.78 ± 0.77**,†,††

* $p < 0.01$, ** $p < 0.001$ experimental groups vs control group.
† $p < 0.001$ diabetic and diabetic exercise groups vs control exercise group.
†† $p < 0.001$ final values vs initial values.

consumption or body weight as compared to the control group. Daily food and water consumption of the diabetic and DE groups were significantly increased with respect to the beginning values and non-diabetic groups.

Blood glucose, lactate and TBARS levels

The mean glucose values are given in Table 2. Blood glucose level was multifold higher in the diabetic groups than in the control group, indicating that hyperglycaemia was sustained in these groups. The glucose level was significantly reduced in diabetic-exercise rats compared to the diabetic group. There was no significant difference in the plasma glucose concentration between the control and exercise groups.

To determine whether this exercise programme was aerobic training, we examined blood lactate levels (Table 2). There was no significant difference between sedentary controls and exercising control groups. On the other hand, lactate values were significantly increased in the diabetic groups compared with the control group, but lactate levels were lower in the DE group compared with the D group.

TBARS values of brains of the studied groups are summarized in Table 2. TBARS levels were found to be elevated in the brains of the diabetic groups. However, brain TBARS levels of the exercise training group were unaltered.

TABLE 2. Plasma glucose and lactate values and brain TBARS measurements of control and experimental groups. Values represent the mean ± S.E.

Group	Glucose (mg/dl)	Lactate (mM/l)	Brain TBARS (nM/g protein)
Control	119.20 ± 5.21	2.11 ± 0.23	1.98 ± 0.09
Control exercise	156.40 ± 11.19	2.21 ± 0.17	2.20 ± 0.38
Diabetic	447.40 ± 10.9***$^{,\#\#}$	7.42 ± 0.57 ***$^{,\#\#}$	3.191 ± 0.39 *
Diabetic-exercise	273.40 ± 40.95 ***$^{,\#,\dagger}$	5.75 ± 0.64 ***$^{,\#\#}$	3.29 ± 0.29 *

TBARS, thiobarbituric acid reactive substances.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ experimental groups vs control group.
$^{\#}$ $p < 0.01$, $^{\#\#}$ $p < 0.001$ diabetic and diabetic exercise groups vs control exercise group.
† $p < 0.001$ diabetic exercise group vs diabetic group.

Latency and amplitude values of VEP components

Differences of VEP parameters were analysed by repeated measures of ANOVA. We did not find significant differences in latencies and amplitudes between the right and left eyes, but we did between groups. The data from stimulating each eye were averaged. The means and standard deviations of peak latencies and peak-to-peak amplitudes of VEP components of all groups are shown in Tables 3 and 4. The mean latencies of P_1, N_1, P_2 and P_3 components were significantly prolonged in the diabetic group compared to the control group. On the other hand, in the exercise group, the mean latencies of all VEP components were unchanged with respect to the control group. In the DE group, the mean latencies of P_1, N_1, P_2 and P_3 components were prolonged compared to control values, but shortened with respect to the diabetic group. Therefore, we conclude that exercise training improved the mean latencies of VEP components which were prolonged because of the effect of diabetes.

P_2N_2 amplitude of the DE group was significantly higher compared to the control and control exercise groups.

Discussion

Animals showed significant loss of body weight and hyperphagia and polydipsia. These results are in accordance with results previously reported after treatment of streptozotocin-diabetic rats (Kumar and Menon 1993; Yargıcoglu et al. 1999; Coskun et al. 2004). Once the food and water intake of the DE group was increased compared to the non-diabetic groups, their energy expenditure and body fat utilization increased due to exercise, and the final result was a reduction of body weight in these animals.

The plasma glucose level was three-and-a-

Table 3. Peak latencies (mean ± s.e.) for each VEP component, determined by averaging the data for both eyes.

Group	Latencies (msec)				
	P_1	N_1	P_2	N_2	P_3
Control	17.90 ± 0.45	31.30 ± 0.89	45.70 ± 1.59	63.50 ± 1.83	91.60 ± 1.30
Control exercise	17.05 ± 0.74	32.09 ± 1.41	45.46 ± 1.83	60.09 ± 1.91	81.55 ± 2.48*
Diabetic	28.85 ± 0.84***,#	48.85 ± 1.14***,#	67.20 ± 2.16***,#	88.3 ± 1.79***,#	122.20 ± 1.83***,#
Diabetic-exercise	23.89 ± 1.34***,#,†	42.0 ± 2.03***,#,†	57.44 ± 1.99***,#,†	74.94 ± 2.75**,#,††	100.56 ± 2.45*,#,††

VEP: visual evoked potentials.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ experimental groups vs control group.
# $p < 0.001$ diabetic and diabetic exercise groups vs control exercise group.
† $p < 0.01$, †† $p < 0.001$ diabetic exercise group vs diabetic group.

Table 4. Peak-to-peak amplitudes (mean ± s.e.) of each VEP component determined by averaging the data for both eyes.

Group	P_1N_1	N_1P_2	P_2N_2	N_2P_3
Control	3.95 ± 0.49	5.51 ± 0.97	6.92 ± 0.93	6.28 ± 1.17
Control exercise	3.06 ± 0.31	3.82 ± 0.39	6.45 ± 0.83	6.44 ± 0.56
Diabetic	5.08 ± 0.55	5.83 ± 0.85	5.76 ± 0.98	6.16 ± 0.61
Diabetic-exercise	3.97 ± 0.47	4.44 ± 0.60	2.71 ± 0.40*,#	4.44 ± 0.52

VEP: visual evoked potentials.
* $p < 0.01$ experimental groups vs control group.
# $p < 0.05$ diabetic exercise group vs control exercise group.

half times higher in the diabetic group than in the control group, indicating that hyperglycaemia was sustained in diabetic rats and this result is consistent with other papers. In the present study, plasma glucose levels of the DE group were found to be decreased compared the non-diabetic groups. Exercise is known to cause an increase in the uptake of glucose in muscle which induces increased GLUT 4 expression and translocation from the intracellular pool (Etgen et al. 1993; Kainulainen et al. 1994). On the other hand, Etgen et al. (1993) found that exercise training results in elevated maximal insulin-stimulated hindlimb glucose uptake. However, the cause and effect relationship between blood glucose concentration and appetite control in diabetic exercising animals has not been clarified.

The speed and the duration of exercise were increased in a graded manner. Blood samples were obtained from the subjects five minutes following the exercise and used for lactic acid determination. Plasma lactic acid level is an indicator of anaerobic threshold which is 4 mM/l for humans (Wilmore and Costill 1994) and 4.2 mM/l for rats (Pilis et al. 1993). Plasma lactate levels measured in the CE group showed that this threshold was not reached. On the other hand, plasma lactic acid levels were higher in the diabetic groups than in the non-diabetic groups, which is in accordance with previous studies (Kandah et al. 1994; Christopher et al. 1995; Mohan and Das 1998).

Our results exhibited that the exercise applied was an aerobic exercise and the exercise programme had no effect on high lactate concentrations seen in the diabetic groups. On the other hand, it was shown that mild-intensity exercise increased glyconeogenic activity and that the conversion of lactic acid into glucose as a glyconeogenic substrate increases with mild-intensity exercise (López-Luna et al. 1998). In the present study, the plasma lactic acid level of the CE group was found to be similar to that of the control group. The slight increase observed in plasma glucose levels in the CE group is independent from the lactic acid level. Exercise in rats is generally accepted as a behavioural and psychological stress factor and after exercise blood catecholamine levels are found to be increased (Kramer et al. 1983). In our study, plasma glucose levels of the CE group were slightly higher than the C group, which supports this finding. However, this difference is insignificant.

VEP component latencies and amplitudes found in our laboratory are in considerable agreement with those found in other laboratories regarding the general trend in normative data (Dyer et al. 1987; Apaydin et al. 1993; Yargicoglu et al. 1999). In the present study, when the data were analysed by an ANOVA with repeated measures, it was found that there were significant differences between groups but not between right and left VEP parameters produced only by stimulation of the right and left eye. As mentioned in previous studies (Mariani et al. 1990), early alterations of VEP data were seen first in the right optic pathway of diabetic patients. This is in contrast to our findings in the present study.

A two-month duration of diabetes mellitus was associated with significant increases in the latencies of VEP. Our finding is also in agreement with previous papers (Anastasi et al. 1985; Yaltkaya et al. 1988; Yargicoglu et al. 1999). These VEP changes may be related to the alterations in electroconductive properties of the myelin sheath induced by various factors such as metabolic disturbance, increased lipid peroxidation, impaired incorporation of acetate and glucose into nerve lipids. However, other as yet unexplored factors can not be ruled out.

In our study, we found shorter VEP latencies in diabetic exercise animals compared to diabetic subjects. To our knowledge, this is the first study to examine exercise-induced VEP changes in diabetic animals. The P_2 component of VEP is believed to reflect the cortical response to the initial afferent volley from the retina through the lateral geniculate nucleus (Kraut et al. 1985; Schroeder et al. 1991). Thus, changes in this portion of the VEP waveform suggest altered function in the 'front end' of the visual system. However, N_2 represents the initial excitatory response in the middle laminae to the visual stimulus, and the subsequent positive peak P_3 was

reported to reflect the excitatory post-synaptic response of pyramidal cells in the upper laminae (Herr et al. 1995). P_2 and N_2 peaks may represent hyperpolarization and depolarization of stellate cells in laminae IV, respectively (Kraut et al. 1985; Herr et al. 1995). It was previously shown that certain toxicological agents, such as carbon disulfide (Graff and Herr 2003) and dichloromethane, 1,3 dichloropropane and 1,2 dichlorobenzene (Herr and Boyes 1997), affect different VEP components via different neurotransmitter levels that generate and modulate VEP peaks. Although the shortened latencies seen in the VEP may, at least in part, be explained by decreased glucose levels or elevated blood flow and changes in synaptic transmission in the cortex, these mechanisms probably do not fully explain the mechanisms of diminished effects of exercise on P_2N_2 amplitude and P_2 and N_2 latencies in diabetic animals.

The exact mechanism of diabetic complications is not clearly defined. However, there has been considerable recent interest in the idea that free radical-induced tissue damage may play a role in the development of complications in diabetes mellitus (Gul et al. 2002). It is well known that free radicals attach to membrane phospholipids, causing their peroxidation. Peroxidation of membrane phospholipids is considered to be a fundamental aspect of free radical damage in the brain due to high lipid contents. Consequently, the formation of toxic lipid peroxidation causes peroxidative damage to the membrane structure and changes in associated enzymes, receptors and physiological functions that may ultimately result in disturbances in neural function. Thus, in this context, the results of our study indicating significant elevation of lipid peroxidation in the brain also supports earlier studies which support the free radical hypothesis in diabetes mellitus (Kumar and Menon 1995; Mooradian 1995; Hartnett et al. 2000; Pasaoglu et al. 2004).

There are a large number of studies showing the mechanisms of exercise and oxidant-induced detriments (Leaf et al. 1997; McBride et al. 1998). The recent study was conducted to investigate how exercise affects the chronic complications of diabetes and to clarify the oxidant mechanism responsible for that effect. While examining the effect of exercise on various organs and systems, the duration and the intensity of exercise should be determined first. Thus, in our study, a mild-intensity exercise program was applied for eight weeks (Kainulainen et al. 1994).

A general trend of higher brain TBARS levels was observed in exercise training groups (CE, DE). However, they did not reach statistical significance. Some studies previously reported contradictory results in which a change in lipid peroxidation was described (Kanter et al. 1993; Lovlin et al. 1997).

From the direct evidence in this study, it can be concluded that physical training may improve the prolonged latencies of VEP observed in diabetic rats and should be recommended for the health of the visual system of Type 1 diabetic patients. Further studies are also necessary to clarify this mechanism.

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