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Retinal energy state in rats with experimental diabetes and axial myopia

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Background: *Elucidating the pathogenesis of diabetic retinopathy (DR) for further development of methods of treatment and prevention of the disease is an important medical and social task for ophthalmologists. The development of DR in the presence of myopia has some special features. In the presence of myopia, the diabetic complications in the retina are less severe than in emmetropia. The mechanisms of this paradoxical impact of eye myopization on the severity of these complications are, however, still unknown.*

Purpose: *To examine the state of retinal energy metabolism based on evaluation of biochemical markers of mitochondrial function (lactate, pyruvate, adenosine triphosphate (ATP) and adenosine diphosphate (ADP) levels and succinate dehydrogenase activity) in rats with streptozotocin (STZ)-induced diabetes that developed in the presence of axial myopia, compared to rats with diabetes alone and those with myopia alone.*

Material and Methods: *High axial myopia was produced in two-week animals by surgically fusing the eyelids of both eyes and maintaining these animals under conditions of reduced illumination for two weeks. A 15 mg/kg intraperitoneal streptozotocin injection for 5 days was used for inducing diabetes mellitus in rats with induced axial myopia and intact rats. Animals in the control group were maintained under conditions of natural illumination. In two months, all rats were euthanized under anesthesia, and their eyes were enucleated. ATP, ADP, lactate, and pyruvate levels were measured in blood and retinal specimens and ATP/ADP ratio and lactate/pyruvate ratio were determined. Succinate dehydrogenase activity was determined in isolated retinal mitochondria. For statistical analysis of biochemical results, Student's t-test was conducted (Statistica software).*

Results: *Rats with diabetes alone exhibited lower retinal and plasma energy metabolism characteristics (ATP, ADP, and succinate dehydrogenase activity), and developed retinal hypoxia, with retinal lactate and pyruvate levels being 1.838-fold and 1.455-fold higher, respectively, and their ratio, 26.5% higher, compared to controls. In animals with STZ-induced diabetes in the presence of axial hypoxia, retinal lactate and pyruvate levels were 20.2% and 15.5% lower, respectively, and their ratio was lower (36.5 versus 38.7), compared to rats with diabetes alone, indicating lower hypoxia in the setting of eye myopization. In addition, in rats with diabetes in the presence of axial hypoxia, plasma and retinal ATP levels were 21.8% and 21.2% higher, respectively, and retinal succinate dehydrogenase activity, 20.8% higher, compared to rats with diabetes alone.*

Conclusion: *In experimental diabetes, an increase in the axial length of the eye (i.e., eye myopization) is accompanied by activation of energy processes and the development of hypoxia adaptation in retinal cells.*

Keywords:

diabetes, diabetic retinopathy, myopia, retina, hypoxia, energy metabolism, experiment

Introduction

Since diabetic retinopathy (DR) is a major cause of irreversible visual impairment and blindness among working-age adults, studies on the pathogenesis, prevention and treatment of this disease are of social importance [1-5].

The development of DR in the presence of myopia has some special features [6-8]. In diabetic retinopathy eyes with myopia, diabetic retinal complications are less severe that in diabetic retinopathy eyes with emmetropia. Each 1-mm increase in the axial length was associated with a decreased risk for non-proliferative DR and proliferative DR (pooled odds ratio [OR], 0.86 and 0.8, respectively). One diopter increase in spherical equivalent and a 1.1-m increase in anterior chamber depth were associated with a decreased risk for DR (OR, 0.9 and 0.32, respectively) [9, 10].

Others [11] reported that DR developed in 40.9% of diabetic patients with myopia, 65% of diabetic patients with emmetropia, and 70.4% of diabetic patients with hyperopia. In addition, they observed no cases of PDR in

diabetic patients with moderate myopia, and no signs of DR in diabetic patients with high myopia. The mechanisms of this paradoxical impact of eye myopization on the severity of diabetic complications in the retina are, however, still unknown.

Tissue hypoxia resulting in deficient energy state is characteristic for vascular pathologies. The processes of supplying energy to retinal cells are important for the vascular pathology of DR, in which metabolic shifts are pathogenetically significant. In proliferative retinopathy, reduced oxygen availability causes compensatory pathological neovascularization [1, 12-14].

Mitochondria are the powerhouses of the cell and are involved in energy metabolism and respiration [15]. Mitochondrial dysfunction severely affects tissue homeostasis. A major function of mitochondria is the production of adenosine triphosphate (ATP), an energy storage molecule. ATP is formed by two major metabolic pathways, glycolysis and oxidative phosphorylation (OXPHOS). The retina has a very high glycolytic and oxidative capacity [12, 16]. Oxygen consumption reflects the activity of the electron transport chain and the production of ATP by mitochondria. The retina is one of the most oxidative tissues in the body, consuming more oxygen than the brain [15-17].

Severe alterations in mitochondrial bioenergetics may promote mitochondrial electron transport chain dysfunction [1, 15]. In mammals, the succinate dehydrogenase (SDH) enzyme is involved in mitochondrial energy production and plays a role in the regulation of the cellular sensitivity to oxygen [18, 19].

Examining the energetic functions of retinal mitochondria in diabetes with eye myopization for elucidating the mechanisms of the protective action of myopia is an important research task that, in addition, has a value for clinical practice.

The purpose of the study was to examine the state of retinal energy metabolism based on evaluation of biochemical markers of mitochondrial function (lactate, pyruvate, ATP and adenosine diphosphate (ADP) levels and succinate dehydrogenase activity) in rats with streptozotocin-induced diabetes that developed in the presence of axial myopia, compared to rats with diabetes alone and those with myopia alone.

Material and Methods

All animal experiments were performed in compliance with the provisions of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Strasbourg, 1986) and Regulations on Working with Experimental Animals approved by the Decree of the Ministry of Health of Ukraine and the Law of Ukraine on Protection of Animals from Cruel Treatment No. 3447-IV dated February 21, 2006, as amended on August 8, 2021.

Fifty-five rats (age, 2 weeks to 10 weeks) were used in the experiment. Four groups were formed: group 1 (axial myopia alone; n = 15); group 2 (diabetes alone; n = 15); group 3 (diabetes in the presence of myopia; n = 15); and group 4 (intact controls; n = 10). High axial myopia was produced in two-week animals by surgically fusing the eyelids of both eyes and maintaining these animals under conditions of reduced illumination for two weeks [20]. Two weeks thereafter, type 2 diabetes mellitus was induced in 15 rats with induced axial myopia and 15 intact rats. A 15 mg/kg intraperitoneal streptozotocin injection for 5 days was used for this purpose. In addition, diabetic rats were fed with high fat diet. The control group was composed of intact animals which were maintained under conditions of natural illumination.

Two months after inducing diabetes, all rats were euthanized under anesthesia, and their eyes were enucleated. Blood and retinal biochemistry studies were performed. ATP, ADP [21], lactate, and pyruvate [21] levels were measured in blood and retinal specimens, and succinate dehydrogenase activity was determined in isolated retinal mitochondria [22]. In addition, ATP to ADP ratio and lactate to pyruvate ratio were calculated. For statistical analysis of biochemical results, Student's t-test was conducted (Statistica software).

Results

Changes in plasma levels of lactate and pyruvate were observed in experimental rats (Table 1). In the diabetes-alone group, plasma levels of lactate and pyruvate were 86.5% and 43.3% higher, respectively, than in controls. Of note was a 1.03-increase in the plasma lactate to pyruvate ratio in this group. In rats with diabetes in the presence of myopia, plasma lactate levels were 18.5% lower, and this difference was significant, whereas plasma pyruvate

Table 1. Levels of plasma lactate and pyruvate (mmol/L) in rats with streptozotocin -induced diabetes in the presence of deprivational myopia

Statistical characteristics	Controls (n = 10)	Diabetes alone (n = 15)	Myopia + diabetes (n = 15)
Lactate			
M±m	2.52±0.17	4.70±0.32	3.83±0.23
%	100.0	186.5	151.2
p	-	<0.001	<0.001
$\%_1$	-	100	81.5
p_1	-	-	<0.05
Pyruvate			
M±m	0.238±0.015	0.341±0.023	0.289±0.018
%	100.0	143.3	121.4
p	-	<0.01	<0.05
$\%_1$	-	100	84.8
p_1	-	-	>0.05
Lactate / pyruvate ratio	10.6	13.8	13.3

Note: n, number of animals; p, significance of difference compared to controls; p1, significance of difference compared to animals with diabetes alone; M, mean value; m, standard error of mean

levels were lower, but not significantly, than in rats with diabetes alone. It is, however, of note that, in rats with diabetes in the presence of myopia, the levels of plasma lactate and pyruvate were statistically significantly higher than in controls.

Retinal lactate and pyruvate levels in rats with diabetes alone were 83.8% and 45.5% higher, respectively (Table 2), with their ratio being 26.5% higher, than in controls. In rats with diabetes in the presence of myopia, retinal lactate and pyruvate levels and their ratio were 46.6 %, 23 % and 19.3 % higher, respectively, than in controls. In addition, in rats with diabetes alone, retinal lactate and pyruvate levels were 20.2 % and 15.5 % higher, respectively, and these differences were significant, whereas the ratio of these parameters was not significantly higher than in rats with myopia alone.

Therefore, our experimental data on the biochemical markers of energy metabolism (namely, plasma and retinal lactate and pyruvate levels) demonstrate the development of hypoxia in the body and retinal neuronal tissue in STZ-induced diabetes in rats. In addition, these parameters were somewhat lower in rats with diabetes in the presence of myopia than in those with diabetes alone, and no shifts in retinal and blood lactate and pyruvate levels were observed in rats with myopia alone.

At the next phase of the study, we determined changes in retinal and plasma levels of ATP and ADP, adenine nucleotide metabolites, in rats with induced myopia and diabetes (Tables 3 and 4). No significant difference was observed in plasma ATP and ADP levels between rats with myopia alone and controls, but in the former rats, the retinal ATP level was 23.6% higher than in controls ($p < 0.05$).

In rats with diabetes alone, plasma ATP and ATF levels were 27.4% and 19.8% lower, respectively, and retinal ATP and ATF levels, 37.3% and 23.7% lower, respectively, than in controls ($p < 0.01$). It is noteworthy that plasma and retinal levels of ATP and ADP were substantially lower in rats with diabetes alone than in those with myopia alone. In rats with diabetes alone, plasma and retinal ATP to ADP ratios were significantly lower than in controls or rats with myopia alone.

In rats with diabetes in the presence of myopia, plasma and retinal ATP levels were 21.8% and 21.2% higher, respectively, than in rats with diabetes alone, which may

Table 2. Levels of retinal lactate and pyruvate (mmol/L) in rats with streptozotocin -induced diabetes in the presence of deprivational myopia

Statistical characteristics	Controls (n = 10)	Diabetes alone (n = 15)	Myopia + diabetes (n = 15)
Lactate			
M±m	5.85±0.42	10.75±0.80	8.58±0.68
%	100.0	183.8	146.6
p	-	<0.001	<0.001
$\%_1$	-	100	79.8
p_1	-	-	<0.05
Pyruvate			
M±m	0.191±0.012	0.278±0.017	0.235±0.016
%	100.0	145.5	123.0
p	-	<0.001	<0.05
$\%_1$	-	100	84.5
p_1	-	-	<0.05
Lactate / pyruvate ratio	30.6	38.7	36.5

Note: similar to Table 1.

Statistical characteristics	Controls (n = 10)	Myopia alone (n = 15)	Diabetes alone (n = 15)	Myopia + diabetes (n = 15)
ATP				
M±m	804.23±62.14	945.77±78.62	583.48±37.04	710.94±46.80
%	100.0	117.6	72.6	88.4
p	-	>0.05	<0.01	>0.05
$\%_1$	-	100.0	61.7	75.2
p_1	-	-	<0.001	<0.05
$\%_2$	-	-	100.0	121.8
p_2	-	-	-	<0.05
ADP				
M±m	352.05±18.45	404.18±26.45	282.34±15.08	324.63±22.07
%	100.0	114.8	80.2	92.2
p	-	>0.05	<0.01	>0.05
$\%_1$	-	100.0	69.9	80.3
p_1	-	-	<0.001	<0.05
$\%_2$	-	-	100.0	115.0
p_2	-	-	-	>0.05
ARP/ADP ratio	2.28	2.34	2.07	2.19

Table 3. Levels of plasma adenosine triphosphate (ATP) and adenosine diphosphate (ADP) (nmol/L) in rats with streptozotocin-induced diabetes in the presence of deprivational myopia

Note: n, number of animals; p, significance of difference compared to controls; p1, significance of difference compared to animals with myopia alone; p2, significance of difference compared to animals with diabetes alone; M, mean value; m, standard error of mean

Statistical characteristics	Controls (n = 10)	Myopia alone (n = 15)	Diabetes alone (n = 15)	Myopia + diabetes (n = 15)
ATP				
M±m	3.24±0.18	3.86±0.23	2.03±0.14	2.46±0.15
%	100.0	123.6	62.7	75.9
p	-	<0.05	<0.001	<0.01
$\%_1$	-	100.0	52.6	63.7
p_1	-	-	<0.001	<0.001
$\%_2$	-	-	100.0	121.2
p_2	-	-	-	<0.05
ADP				
M±m	0.856±0.062	0.961±0.076	0.653±0.050	0.704±0.057
%	100.0	112.3	76.3	82.2
p	-	>0.05	<0.05	>0.05
$\%_1$	-	100.0	68.0	73.3
p_1	-	-	<0.01	<0.05
$\%_2$	-	-	100.0	115.6
p_2	-	-	-	>0.05
ARP/ADP ratio	3.79	4.02	3.11	3.49

Table 4. Levels of retinal adenosine triphosphate (ATP) and adenosine diphosphate (ADP) (μmol/g) in rats with streptozotocin-induced diabetes in the presence of deprivational myopia

Note: similar to Table 3.

Statistical characteristics	Controls (n = 10)	Myopia alone (n = 15)	Diabetes alone (n = 15)	Myopia + diabetes (n = 15)
M±m	87.64±5.23	105.52±6.48	63.45±4.37	76.65±4.53
%	100.0	120.4	72.4	87.5
p	-	<0.05	<0.01	>0.05
$\%_1$	-	100.0	60.1	72.6
p_1	-	-	<0.001	<0.01
$\%_2$	-	-	100.0	120.8
p_2	-	-	-	<0.05

Table 5. Activity of mitochondrial succinate dehydrogenase in the retina (nkatal/g) in rats with streptozotocin-induced diabetes in the presence of deprivational myopia

Note: similar to Table 3.

indicate certain activation of energy processes and the development of hypoxia adaptation in retinal cells.

Studies on succinate dehydrogenase enzyme activity in the retinal mitochondria of experimental animals enable objective functional assessment of the organelles responsible for the production of energy (ATP molecules) in retinal neuronal cells. The results of these studies are presented in Table 5. Retinal mitochondrial activity of succinate dehydrogenase was 20.4% higher in rats with myopia alone compared to controls. In rats with diabetes alone, the retinal mitochondrial activity of succinate dehydrogenase was 27.6% lower compared to controls ($p < 0.01$), and 39.9 % lower compared to animals with myopia alone ($p < 0.001$).

In rats with diabetes in the presence of myopia, the retinal mitochondrial activity of succinate dehydrogenase was 20.8% higher than in rats with diabetes alone. These data also indicate activation of retinal energy metabolism.

Therefore, hypoxia markers, retinal and plasma lactate and pyruvate, were found to be increased in rats with diabetes alone, but decreased in rats with diabetes in the presence of myopia. Retinal energy parameters (ATP levels and succinate dehydrogenase activity) were found to be increased in rats with diabetes in the presence of myopia, but decreased in diabetic emmetropic rats.

Discussion

The results of this experimental study showed the development of retinal hypoxia, with higher retinal levels of lactate and pyruvate, biochemical markers, as well as their ratio, in all rats with STZ-induced diabetes than in controls. In addition, these parameters were statistically significantly lower in rats with diabetes in the presence of myopia than rats with diabetes alone, indicating a decrease in the amount of hypoxia with an increase in the axial length of the eye (a myopization of the eye).

Lactate is a characteristic of bioenergetic hypoxia and a major marker of mitochondrial dysfunction. It is believed to be an early prognostic marker of low oxygen delivery because it is commonly found to be increased earlier than other symptoms of low oxygen delivery. Lactic acid accumulation is observed when the mitochondrial glucose breakdown is greater than pyruvate oxidation. This is seen in mitochondrial dysfunction due to a decrease in cellular oxygen level. When oxygen delivery to cells is reduced, they use a less effective energy production process known as anaerobic metabolism, with glucose cleavage resulting in the production of ATP. Lactate is the major byproduct of this anaerobic process. Markedly elevated plasma lactate increase above (>3 mmol/l) suggests the presence of mitochondrial dysfunction [23-25].

Pyruvate is an intermediate metabolite playing an important role in the metabolism of amino acids and carbohydrates in the tricarboxylic acid cycle, fatty acid beta oxidation and the electron transport chain in mitochondria. The prognostic significance of this metabolite is, however, limited if lactate content is not determined. Lactate to pyruvate ratio characterizes the ratio between glycolytic and oxidative carbohydrate transformations.

In the current study, in rats with STZ-induced diabetes, we found not only hypoxia but also reduced retinal and plasma levels of ATP and ADP (adenine nucleotide metabolites) and succinate dehydrogenase enzyme activity, markers of cellular energy capacity. In rats with STZ-induced diabetes, eye myopization was accompanied by some improvement in energy status and increase in these parameters. In rats with diabetes in the presence of axial myopia, biochemical energy markers and mitochondrial enzyme activity in the retina were found to be significantly increased compared to rats with diabetes alone.

ATP and ADP are known to be important regulators of insulin secretion, which is stimulated by the level of glucose. In aerobic cells, phosphorylation capacity is regulated through the mechanisms which are characteristic of mitochondrial metabolism and cause compensatory changes in the electron transport chain. Changes in the mitochondrial energetic metabolism may cause impairment in the entire mitochondrial electron transport chain [1, 15, 26]. Reduced ATP levels and structural and functional abnormalities in the apparatus of cellular membrane receptors were found in patients with types 1 and 2 diabetes [27]. In addition, a reduced ATP to ADP ratio in erythrocytes diabetic patients has been reported [28].

Succinate dehydrogenase is a key enzyme in cell energy metabolism. Impaired succinate dehydrogenase activity indicates the presence of mitochondrial dysfunction. The enzyme is a component of the mitochondrial electron transport chain and Krebs cycle [19].

We have previously [8] found that, in animals with STZ-induced diabetes in the presence of myopia, there were ultrastructural changes in the retinal pigment epithelium, which indicated somewhat increased protein synthesis and energy production within the cells. The results of current biochemical studies also demonstrate statistically significantly higher energy production and lower hypoxia in the retina of rats with diabetes in the presence of myopia compared to rats with diabetes alone.

Findings of our experimental disease studies on the potential metabolic mechanisms of the protective effect of eye myopization on the development of diabetic complications in the retina will facilitate further understanding of the pathogenesis of diabetic retinopathy in patients with diabetes in the presence of myopia.

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Disclosures

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