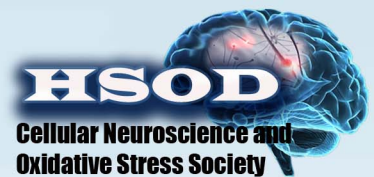
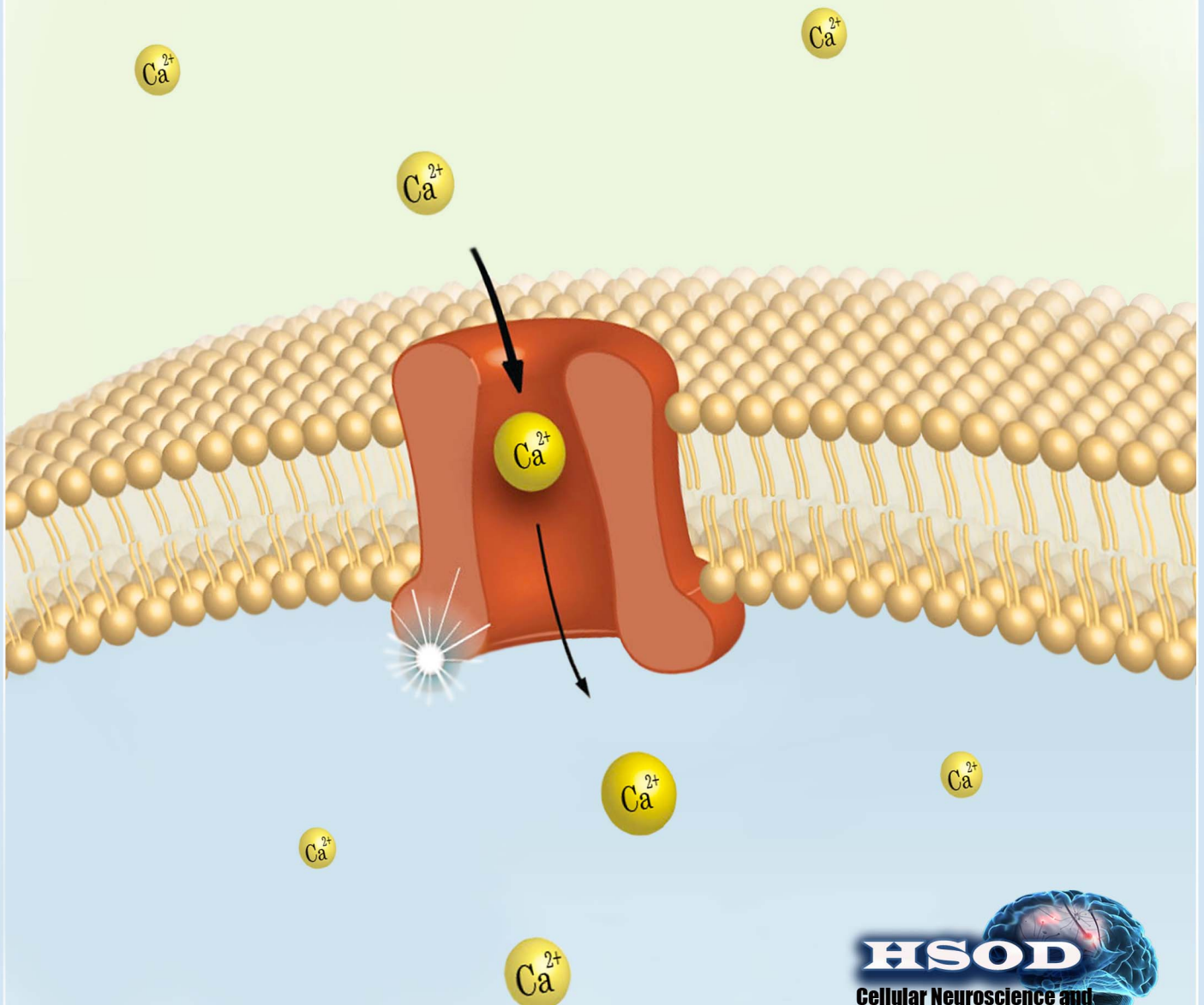


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[CONTENTS]

- 588 Melatonin reduces lens oxidative stress level in STZ-induced diabetic rats through supporting glutathione peroxidase and reduced glutathione values
Mehmet Cemal Kahya, Mustafa Nazirođlu
- 595 Is Hypericum perforatum agonist or antagonist of TRPC6 in neurons?
Mustafa Nazirođlu

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Department of Biophysics and Neurosciences,
Medical Faculty, Suleyman Demirel University,
Isparta, Turkey.
Phone: +90 246 211 37 08. Fax: +90 246 237 11 65
E-mail: mustafanaziroglu@sdu.edu.tr

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Melatonin reduces lens oxidative stress level in STZ-induced diabetic rats through supporting glutathione peroxidase and reduced glutathione values

Mehmet Cemal Kahya¹, Mustafa Nazıroğlu^{2*}

¹Department of Biophysics, Faculty of Medical Faculty, İzmir Katip Çelebi University, İzmir, Turkey

²Department of Biophysics, Faculty of Medical Faculty, Suleyman Demirel University, Isparta, Turkey

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Abstract

Hyperglycemia plays a critical role in the development and progression of diabetic cataract oxidative injuries via the increased reactive oxygen species (ROS) production. Melatonin has been considered a potent strong antioxidant that detoxifies a variety of ROS in many metabolic diseases. The present study was conducted to explore whether melatonin administration protects against diabetic lens oxidative injuries through modulation of reduced glutathione (GSH) and glutathione peroxidase (GPx) systems in streptozotocin (STZ)-induced diabetic rats.

Thirty two rats were equally divided into four groups as control, STZ, melatonin and STZ and melatonin. The third and fourth groups received intraperitoneal 10 mg/kg melatonin for 2 weeks. For induction of diabetes in the second and fourth groups, intraperitoneal STZ (45 mg/kg) was given.

Lipid peroxidation (MDA), total oxidant status and intracellular ROS levels in the lens were increased in STZ group, although they were decreased by the melatonin treatment. GPx activity, GSH concentration and total antioxidant status (TAS) were lower in STZ group than in control. However, the GSH concentration, GPx activity and TAS levels were recovered by melatonin. TAS was also higher in the melatonin group than in the STZ and melatonin groups.

In conclusion, the present study shows that melatonin induced protective effects against diabetes-induced lens oxidative injury through up-regulation of the GSH and GPx values but down-regulation of oxidative stress.

Keywords: Diabetes; Glutathione; Lens; Lipid peroxidation; Melatonin.

Introduction

Diabetes mellitus (DM) is a worldwide general endocrine disorder. Several physiological functions of the body including lens are affected by DM.

*Author for correspondence (Present address):

Prof. Dr. Mustafa NAZIROĞLU

Visiting Professor, Division of Cell Signaling, (National Institute for Physiological Sciences), National Institutes of Natural Sciences Higashiyama 5-1, Myodaiji, Okazaki, Aichi 444-8787 JAPAN

Phone: +81-80-4885-9476, Fax: +81-564-59-5285,

e-mail: mnazirog@nips.ac.jp

List of Abbreviations;

DM, diabetes mellitus; GPx, glutathione peroxidase; GSH, reduced glutathione; MDA, malondialdehyde; STZ, streptozotocin; TAS, total antioxidant status; TOS, total oxidant status

It is primarily characterized by high blood glucose levels (hyperglycemia) induced by insulin insufficiency (Singh and Jialal, 2008). In addition to body weight loss, vascular devastation and nephropathy, eye diseases such as cataract and retinopathy might be induced by DM (Srivastava et al., 2011; Akash et al., 2015). In addition, overproduction of reactive oxygen species (ROS) through up-regulation of aldose reductase and down-regulation of antioxidant systems has been reported in DM (Srivastava et al., 2011; Nazıroğlu et al., 2012; Balestri et al., 2015). Non-enzymatic and auto-oxidative glycosylation metabolic stress through activation of energy metabolism and activity of the sorbitol path in DM are activated by overproduction of ROS (Singh and Jialal, 2008).

Melatonin (*N*-acetyl-5-methoxytryptamine) hormone is mainly secreted by pineal gland and most of physiological functions in the body are affected by the hormone (Ekmekcioglu, 2006; Sharafati-Chaleshtori et al., 2017). A main role of the hormone in the body is antioxidant role and evidences from studies proved a key role of melatonin in the ROS production through regulation of glucose metabolism in the pathogenesis of diabetes (Salmanoglu et al., 2016; Kahya et al., 2017). Positive role of melatonin on blood antioxidants levels such as reduced glutathione (GSH) level and glutathione peroxidase (GPx) activity in several diseases except diabetes was reported (Urata et al., 1999; Reiter et al., 2001). Furthermore, a recent experiment with limited analyses showed that lens oxidative stress levels were diminished in streptozotocin (STZ)-induced diabetic rats by the melatonin treatment (Khorsand et al., 2016). Therefore, melatonin may reduce oxidative stress in lens oxidative stress and antioxidant levels.

To our knowledge, there is no report on melatonin, GSH and GPx values in the lens of STZ-induced diabetic rats. Thus, the present study aimed to investigate whether or not melatonin has protective effects on diabetes-induced lens oxidative damage in rats.

Materials and Methods

Animals

We used thirty two (170±10 g) adult Wistar albino rats (3 months old). The project was approved by the Local Experimental Animal Ethical Committee of Suleyman Demirel University (SDU) (Protocol number:

22.05.2014-04). The animals were maintained and used according to the Animal Welfare Act and the Guide for the Care and Use of Laboratory. They were housed two per cage where the room temperature (22°C) and humidity (60%) were under control on a 12 hours light-dark cycle, and commercial feed and tap water were accessible by the animals.

Study Groups

The rats were equally divided into four groups as follows (n=8):

Control group: The group received 0.9 % w/v saline and (0.2 ml) DMSO via intraperitoneal injection.

STZ group: Diabetes was induced by a single dose (45 mg/kg) of intraperitoneal STZ. The blood glucose levels were measured 4-5 days after the STZ injection by using a glucometer (eBsensor, Visgener Inc., Hsinchu City, Taiwan). Presence of diabetes was detected by increased blood glucose levels (≥ 20 mmol/l) (Kahya et al., 2017).

Melatonin group: The rats in the group received melatonin (10 mg/kg/day) via intraperitoneal injection for 14 days. Melatonin was dissolved in DMSO (1% w/v) before injection (Dilek et al., 2010).

Diabetes (STZ)+melatonin group: Rats administrated with intraperitoneal melatonin (same as Melatonin Group) after STZ treatment.

After 12 hours of last melatonin dose administration, all rats were sacrificed for taking lens samples.

Preparation of lens samples

Lens of the rats was prepared as described in a previous study (Tök et al., 2014). Lenses were washed twice with cold saline solution, placed into glass bottles, labeled and stored in a deep freeze (-33 °C) until processing (maximum 3 months). After weighing, the lenses was cut into small pieces by using scissors, and homogenized in 5 volumes (1:5, w/v) of ice-cold Tris-HCl buffer (50 mM, pH 7.4), by a ultrasonic homogenization (SONOPULS HD 2070, Bandelin Electronic, Berlin, Germany). Then they were centrifuged (5 minutes at 4000 rpm). The supernatant was used for the analyses. All preparation procedures were performed on ice.

Lipid peroxidation determinations

Lipid peroxidation as malondialdehyde (MDA) level in the lens homogenate was measured with the thiobarbituric-acid reaction by the method of Placer et al., (1966). The level of MDA in the lens was expressed as $\mu\text{mol/g}$ protein.

Intracellular ROS production analyses

The fluorescence intensity of Rhodamine 123(Rh 123) is a non-fluorescent in the lens homogenate sample was measured (excitation: 488 nm and emission: 543 nm in an automatic microplate reader (Infinite pro200; Tecan Austria GmbH, Groedig, Austria) (DU et al., 2012). Treatments were carried out in triplicate. Data are presented as fold-increase over the pretreatment level.

Reduced glutathione (GSH), glutathione peroxidase (GPx) and protein assays

The GSH content of the lens was measured at 412 nm according to Sedlak and Lindsay method (1968). GPx activity of the lens was measured spectrophotometrically at 37 °C and 412 nm using method of the Lawrence and Burk (1976). GPx activity and GSH level in the lens were expressed as IU/g protein and $\mu\text{mol/g}$ protein, respectively. The protein content in the lens was measured by using Bradford's method.

Total Antioxidant status (TAS) and total oxidant status (TOS) analyses

The TAS and TOS levels were measured calorimetrically using the TAS and TOS commercial kit (Mega Tıp Inc, Gaziantep, Turkey) (Erel, 2004). The results in the lens were expressed in $\mu\text{mol H}_2\text{O}_2$ equivalent/g protein ($\mu\text{mol H}_2\text{O}_2$ equiv/ g prot).

Statistical analysis

The results are expressed as means \pm standard deviation (SD), was used for the statistical treatment of the data. The Mann-Whitney U-test was used to establish the significance of differences among the four groups by using the statistical program (17.0, SPSS Inc. Chicago, Illinois, USA). The significance level was set at $p < 0.05$.

Results

Lipid peroxidation (MDA), total oxidant status (TOS) and intracellular ROS results

Lipid peroxidation as MDA and TOS occurs in lipids, protein and nucleic acids and peroxidation (that are all associated with cataract formation) are widely used in acting as a biomarker of oxidative stress (Placer et al., 1966; Wang et al., 2016). Rh 123 is a non-fluorescent, non-charged dye that easily penetrates cell membranes (DU et al., 2012). Once inside the cell, DHR 123 becomes fluorescent upon oxidation to Rh 123, with the fluorescence being proportional to ROS generation and fluorescence intensity of the dye indicated intracellular ROS levels.

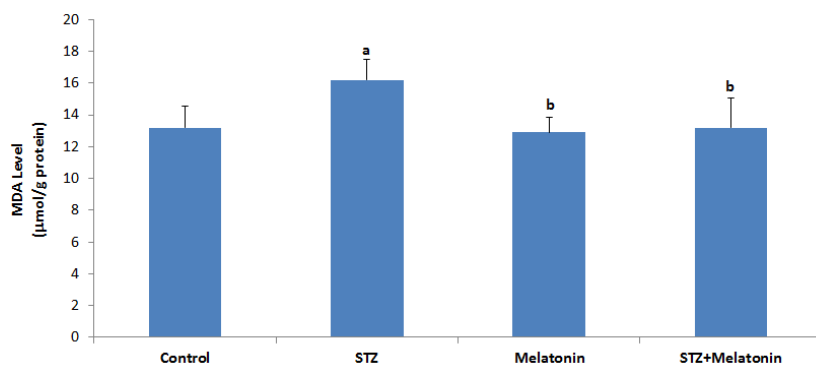


Figure 1. The effects of melatonin on lipid peroxidation (MDA) levels in lens of STZ-induced diabetic rats (mean \pm SD and $n=8$). ^a $p < 0.05$ versus control. ^b $p < 0.05$ versus STZ group.

The mean lens MDA, TOS and ROS levels in four groups were shown in Figures 1, 2 and 3, respectively. The results showed that MDA ($p < 0.05$), TOS ($p < 0.001$) and ROS ($p < 0.001$) levels in the lens samples in the STZ group were significantly higher than the control. Hence, oxidative stress level in the lens of the rats was increased by STZ administration. However, the MDA, TOS and ROS levels were decreased in the fourth group by the melatonin treatments. The lens MDA ($p < 0.05$), TOS ($p < 0.001$) and ROS ($p < 0.001$) levels in the melatonin and STZ+melatonin groups were significantly lower than the STZ group.

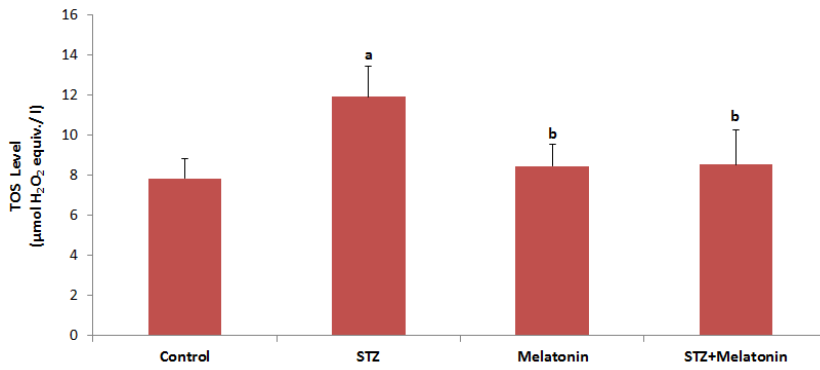


Figure 2. The effects of melatonin on total oxidant levels (TOS) in lens of STZ-induced diabetic rats (mean ± SD and n=8). ^a p < 0.001 versus control. ^b p < 0.001 versus STZ group.

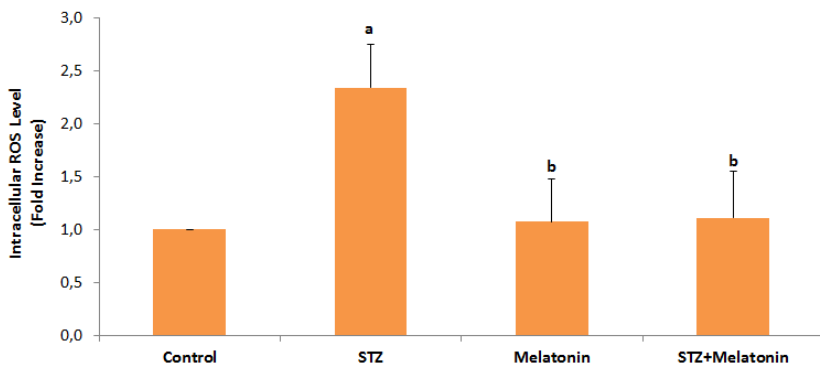


Figure 3. The effects of melatonin on intracellular ROS production in lens of STZ-induced diabetic rats (mean ± SD and n=8). ^a p < 0.001 versus control. ^b p < 0.001 versus STZ group.

Glutathione peroxidase (GPx) activities, total antioxidant status (TAS) and reduced glutathione (GSH) results

Superoxide radical is converted to hydrogen peroxide by catalytic effects of superoxide dismutase. Then the hydrogen peroxide is converted to water by GPx which is uses GSH as a substrate (Sen and Packer, 2000). Therefore, we investigated effects of melatonin on the antioxidant GSH and GPx values in the lens homogenate of diabetic rats.

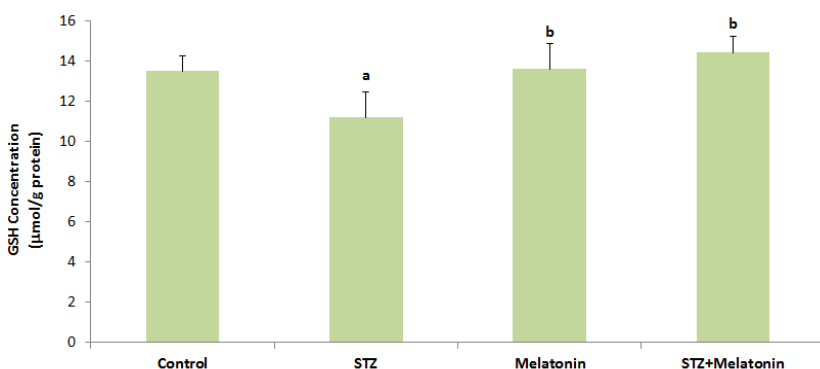


Figure 4. The effects of melatonin on reduced glutathione (GSH) level in lens of STZ-induced diabetic rats (mean ± SD and n=8). ^a p < 0.05 versus control. ^b p < 0.05 versus STZ group.

The mean GSH concentration and GPx activity results in four groups were shown in Figures 4 and 5, respectively. The results showed that the GSH concentration and GPx activity were significantly (p < 0.05) lower in STZ group as compared to control. However, their values were increased in the lens of the melatonin and STZ+melatonin groups the melatonin administrations (p < 0.05).

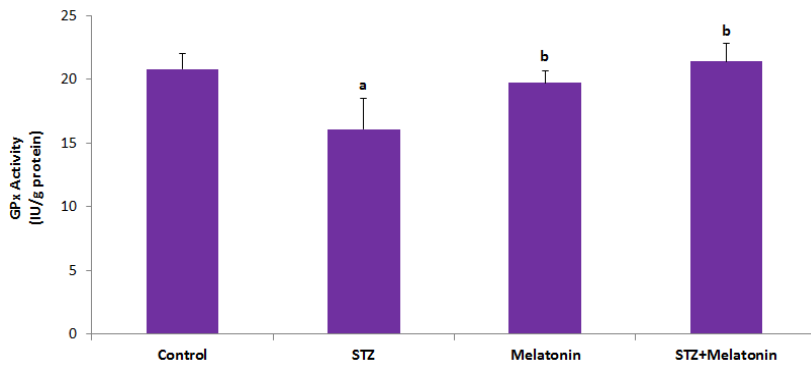


Figure 5. The effects of melatonin on glutathione peroxidase (GPx) activity in lens of STZ-induced diabetic rats (mean \pm SD and n=8). ^a $p < 0.05$ versus control. ^b $p < 0.05$ versus STZ group

The mean TAS results in the four groups were shown in Figure 6. The TAS levels were significantly ($p < 0.05$) lower in STZ group than the control. However, the decreased TAS level was increased by melatonin treatment. On the other word, the TAS results in the melatonin and STZ+melatonin groups were significantly higher than in STZ ($p < 0.001$) and control ($p < 0.05$ and $p < 0.001$) groups.

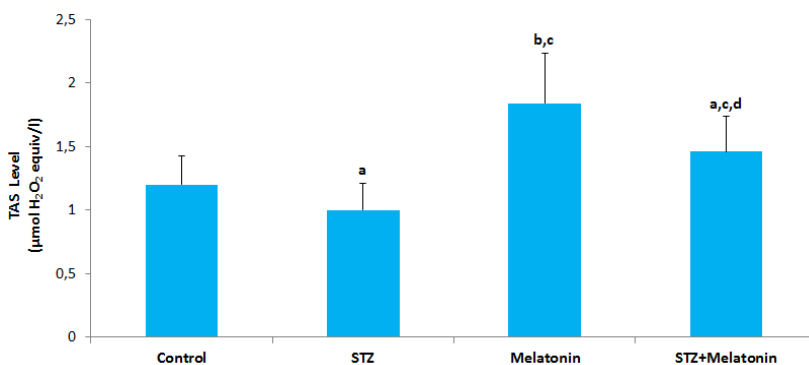


Figure 6. The effects of melatonin on total antioxidant status (TAS) in lens of STZ-induced diabetic rats (mean \pm SD and n=8). ^a $p < 0.05$ and ^b $p < 0.001$ versus control. ^c $p < 0.001$ versus STZ and control groups. ^d $p < 0.001$ versus melatonin group.

Discussion

We observed that oxidative stress markers (MDA, ROS and TOS) of the currents study in the lens were increased by diabetes induction, although GPx activity and GSH level were decreased by the diabetes. Hence, diabetes induction in the lens of animals is characterized by increased oxidative stress markers and decreased TAS, GSH and GPx level. However, the oxidative stress marker levels were decreased the melatonin treatment, although GPx activity, GSH and TAS levels were increased by the treatment. To the best of our knowledge, the results of current study is the first to compare the melatonin with a reference (Khorsand et al., 2016) to its effects on oxidative stress and antioxidant GSH redox system in experimental diabetes-induced oxidative lens injury in rats.

Advanced glycation end products, increased levels of oxidative stress, elevated activities of polyol pathway enzymes, and decreased antioxidant scavenger system in lens have main roles in induction of diabetic cataract of human and experimental animals (Kovacic and Somanathan, 2008; Akash et al., 2015). Results of several reports have indicated the beneficial influence of aldose reductase inhibitors on polyol pathway and antioxidant defense system with cataract induction in human and experimental animals (Balestri et al., 2015). In the current study, we observed increased levels of TOS, ROS and MDA in lens of diabetic rats. Our results are in agreement with those of recent studies that oxidative stress plays a major role in the development of cataract (Tök et al., 2014; Khorsand et al., 2016). Similarly, decreased GPx activity and GSH levels are

reported in diabetes-induced cataract (Suresha and Srinivasan, 2013; Kador et al., 2014; Khorsand et al., 2016).

In the current study, we observed decrease role of melatonin on MDA levels in the lens of experimental diabetes-induced rats. This study also provides evidence that melatonin is most able to protect the lens against diabetes-induced ROS production by directly or indirectly (supporting TAS and GSH levels, and GPx activity). In consequence, melatonin supplementation may increase the antioxidant GSH capacity of diabetic rats or prevent diabetes-induced oxidative damage either directly through its antioxidant action or indirectly through binding to the cell membrane (Reiter et al., 2001).

In the current study, we observed GSH and GPx values were decreased in the lens of STZ-induced diabetic rats by the diabetes induction, although the values were increased in the lens by the melatonin treatment. Selenium containing GPx enzyme is a member of the group of thiol redox cycle antioxidant enzyme and hydrogen peroxide and alkyl hydroperoxides are detoxified in cells by the GPx enzyme (Miranda-Díaz et al., 2016). GSH plays an important role in protecting cells against hydroxyl radical and singlet oxygen. It acts a source of GPx by maintaining the reduced state of GPx thiol groups (Sen and Packer, 2000). Increase of GSH level through activation of the enzyme γ -glutamyl-cysteine synthetase increased by the melatonin treatment was reported (Urata et al., 1999). Reduced mitochondrial oxidative stress and increase of GSH levels through increase of gene expression of GPx, GSH reductase, catalase, and superoxide dismutase by melatonin treatment were also reported (Reiter et al., 2001). Strong antioxidant role of melatonin has been also shown in oxidative stress-induced diseases of human (Sharafati-Chaleshtori et al., 2017). Hence, result of the study confirmed the idea that diabetic lens TAS, GSH levels and GPx activity were increased through inhibition of diabetes-induced mitochondrial oxidative stress in lens of diabetic rats by the melatonin treatment. Similarly, decreased MDA level and increased GSH level in lens of diabetic rats were reported by Khorsand et al., (2016).

In conclusion, our data indicated that melatonin treatment decreased the glucose-related oxidative stress damage, which was associated with enhanced GPx

activity, TAS and GSH levels, and its downstream oxidative stress in the lens of diabetic rats. Therefore, these data suggest the melatonin as a strong antioxidant has preclinical potential for treating diabetic cataract.

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Declaration of interest:

There is no conflict interest in the study.

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Principal Contact

Prof. Dr. Mustafa NAZIROGLU / Editor in Chief
Suleyman Demirel University, Faculty of Medicine, Department of Biophysics
32260 Cunur - Isparta / TURKEY
Phone: +90 246 2113641 Fax: +90 246 2371165
mustafanaziroglu@sdu.edu.tr
biophysics@sdu.edu.tr