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Melatonin Administration Increases GLUT4 Expression İn Heart Tissue Of Aged Diabetic Rats

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Poster # PC43

AIM:

Heart consumes more energy than any other organ. The etiopathogenesis of diabetic cardiomyopathy has been attributed to the impairment of cardiac metabolism secondary to decreased glucose uptake and metabolism in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). The impaired utilization of glucose in cardiomyocytes is accompanied by downregulation of glucose transporters (GLUTs). Cardiac cells are expressed as 2 families of glucose transporters: GLUTs and SGLTs. In human heart, GLUT4 is the major isoform that represents approximately 70% of the total glucose transporters. Expression of GLUT4 and membrane translocation is decreased in the heart muscle of animals with both type 1 and type 2 diabetes mellitus.

Melatonin has been shown to modulates GLUT4 expression in cell culture medium. In several studies performed using pinealectomized animal models, researchers have reported that the absence of melatonin reduced glucose transporter 4 (GLUT4) gene expression, which subsequently induced peripheral and central insulin resistance and glucose intolerance, finally developing diabetes mellitus. Significant alleviation of these pathological abnormalities after melatonin therapy is administered indicates that melatonin plays a critical role against the development of diabetes. Reporting of reduced GLUT4 expression in heart tissue of hyperthyroid rats treated with melatonin supplementation also indicates an inevitable association between melatonin and cardiac GLUT4 expression.

Although the relationship between melatonin and GLUT 4 expression has been reported in many studies, there are scarcely any reports investigating the effects of melatonin supplementation on GLUT4 expression in heart tissue of diabetic rats.

The aim of this study is to investigate how melatonin supplementation affects GLUT 4 levels in heart tissue in a diabetic elderly female rat model.

METHODS:

The study was performed on female aged rats (16 months old) which were provided by The Experimental Medicine Research and Application Center of Selcuk University. The study protocol was approved by the Selcuk University Experimental Medicine Researchand Application Center ethics committee of the latter. In the study conducted on 24 female old Wistar rats the animals were divided into 4 groups in equal numbers.

Group 1:General Control Group: the group which was not subjected to any procedure and fed on a normal diet.

Group 2:Melatonin-Supplemented Control Group: the group fed on a normal diet and supplemented with 5 mg/kg/day subcutaneously melatonin for 4 weeks.

Group 3:Diabetes Group: the group in which diabetes was induced by subcutaneous injection of “40 mg/kg” streptozotocin (STZ).

Group 4: Melatonin-Supplemented Diabetic Control Group: the group in which diabetes was induced by subcutaneous injection of “40 mg/kg” streptozotocin (STZ) and which was supplemented with 5 mg/kg/day subcutaneously melatonin for 4 weeks.

Inducement of Diabetes in Experimental Animals

In order to induce diabetes, 12 rats were picked as the diabetes groups. The rats were injected with 40 mg/kg subcutaneous streptozotocin (STZ) “Sigma, S-0130”. 6 days after injection, blood glucose levels of the animals were determined from the tail vein using a diagnostic glucose kit. The animals whose blood glucose rose to or above 300 mg/dlt were accepted as diabetic.Also, to rats, 5mg/kg/day resveratrol (intraperitoneal) and melatonin (subcutaneously) were given for 4 weeks.

Melatonin Supplementation

After dissolving 40 mg of melatonin (Sigma M-5250) in 3 ml pure ethanol, this suspension was sealed and stored in dark in the deep freeze until the time of use. From the stock solution 0.1 ml was added 0.4 ml NaCl (5 mg/kg/day) and injected to the rats through the intraperitoneal route at 09.00 a.m. Melatonin supplementation was carried out at the same hours for 4 weeks.

Biochemical Analyses:

At the end of the experiment, in cardiac tissue samples taken under general anesthesia as well GLUT 4 protein gene expression were determined by PCR.

Statistical Evaluations

Computer package software was used in the statistical evaluation of results. Arithmetic means and standard deviations of all parameters were calculated. Variance analysis was used to determine differences between groups. The Least Significance Difference (LSD) test was employed to compare group means in variance analysis results which were found significant. Differences for which $p<0.05$ were considered significant.

RESULTS:
The lowest heart tissue GLUT4 levels were determined in the diabetes group (G3), ($p<0.05$). However, melatonin supplementation normalized decreased cardiac GLUT 4 expression in diabetic rats ($p<0.05$, Table 1).

Table 1: GLUT 4 gene expression values of the study groups in heart tissue

Groups	N	GLUT4 gene expression ($2^{-\Delta CT}$)
K	6	0,055±0,009[a]
KM	6	0,058±0,014[a]
D	6	0,0009±0,0003[b]
DM	6	0,055±0,004[a]

*Means with different superscripted letters in the same column are statistically significant (a>b) ($p<0,005$).

CONCLUSION: The results of present study indicated that melatonin administration is increases the expression of GLUT 4 in heart tissue of aged diabetic rats. This finding may be the first study to investigate and report that melatonin supplementation increases cardiac GLUT4 expression in a diabetic elderly female rat model.