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Melatonin Administration Increases The Expression of Sirtuin-1 and Pgc-1α in Heart Tissue of Rats with Aged-diabetic.

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Poster # PC42

AIM:

In the Sirtuin family, SIRT1 and SIRT3 proteins are suggested to be of critical importance in the cardiovascular system. SIRT1 is particularly noteworthy because of its effect on cardiomyocyte survival and growth under stress, which is associated with ventricular hypertrophy.

Melatonin, chemically N-acetyl-5-methoxytryptamine, has been proved to exert its protective properties in a variety of cardiovascular diseases. The silent information regulator 1 (SIRT1) is considered to play a role in the cardioprotective effects of melatonin. It has been reported that melatonin can reduce myocardial ischemia-reperfusion injury in both non-diabetic and diabetic animals through SIRT1 activation. Decreased SIRT1 expression was found in diabetic hearts while, increased SIRT1 expression exerts its beneficial effects on cardiac tissue by reducing oxidative stress and endoplasmic reticulum stress.

Many of the adaptive effects of SIRT1 signalling on organellar in health and cellular stress are mediated or facilitated by its action to deacetylate peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α), a member of a family of transcription coactivators that play a central. Like SIRT1, PGC-1α exerts cardioprotective effects in numerous experimental models as a result of its actions to promote mitochondrial biogenesis and antioxidant mechanisms, while suppressing inflammation. Melatonin induced activation of, Sirtuin 1 (SIRT1) along with PGC 1α, plays a key role in the regulation of mitochondrial biogenesis.

METHODS:

The study was performed on female aged rats (16 months old) which were provided by The Experimental Medicine Research and Application Center of Selçuk 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 study animals were sacrificed under general anesthesia, heart tissue samples obtained and SIRT1 and PGC-1alpha 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 SIRT1 expression in heart tissue were found in the diabetes group ($p<0.05$, Table 1). Heart tissue SIRT1 expression in groups 1,2 and 4 was higher than the levels in groups 3 ($p<0.05$, Table 1).

Groups 1,2 and 4 had the highest heart PGC-1alpha expression values ($p <0.05$). The lowest PGC-1alpha expression values in heart tissue were found in the diabetes group ($p<0.05$, Table 2).

Table 1: SIRT1 expression values of the study groups in heart tissue

Groups	N	SIRT1 gene expression ($2^{-\Delta CT}$)
G1 Control	6	0,122±0,018[a]
G2 Melatonin Control	6	0,068±0,030[a]
G3 Diabetes	6	0,004±0,001[b]
G4 Diabetes + Melatonin	6	0,073±0,002[a]

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

Table 2: PGC-1α expression values of the study groups in heart tissue

Groups	N	PGC-1α gene expression ($2^{-\Delta CT}$)
G1 Control	6	1,500±0,133[a]
G2 Melatonin Control	6	1,496±0,145[a]
G3 Diabetes	6	0,057±0,021[b]
G4 Diabetes + Melatonin	6	1,505±0,126[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 increasing the expression of sirtuin-1 and PGC-1 α in heart tissue of aged diabetic rats. Chronic melatonin therapy can cure the reduction in sirtuin-1 and PGC-1 α expression caused by diabetes in the aged rat model. Chronic melatonin supplementation has a protective effect on the diabetic rat heart.