Melatonin ameliorates cardiac remodelling in fructose-induced metabolic syndrome rat model by using genes encoding cardiac potassium ion channels

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Received: 27 April 2021 / Accepted: 27 June 2021 / Published online: 4 August 2021
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Abstract

Background Metabolic syndrome comprises a group of disorders, including cardiac abnormalities. Ventricular arrhythmias observed in metabolic syndrome are due to the impaired ventricular repolarization. This study aims to determine the effects of melatonin on cardiac ventricular repolarization in metabolic syndrome rat model.

Methods and results Sprague–Dawley rats were divided into control (n = 8), melatonin (n = 8), metabolic syndrome (n = 8) and metabolic syndrome + melatonin (n = 8) groups. Fructose (200 g/l/day) was added into the drinking water during 8 weeks of rats to induce metabolic syndrome model. In the last two weeks, melatonin (20 mg/kg/day) was administered via oral gavage. Blood pressure measurements and ECG recordings were taken at three different times. Blood and left ventricular tissue samples were harvested and the KCNQ1,3 and KCNH2 gene expressions were analysed by qRT-PCR method. We observed insulin resistance, hyperglycemia, dyslipidemia and higher systolic blood pressure in metabolic syndrome group (p < 0.01, for all). Prolonged QT interval was observed in metabolic syndrome group (p < 0.001). The expression levels of the KCNQ genes encoding the Kv7 channel was significantly reduced, however KCNH2 gene which encodes Kv11.1 channel was increased in metabolic syndrome group compared to control group (p < 0.05, p < 0.001, respectively). Melatonin significantly normalised the prolongation on QT interval in metabolic syndrome group (p < 0.001) and the expressions of the KCNQ (p < 0.002) and KCNH2 genes (p = 0.003).

Conclusions The present study revealed that melatonin had ameliorative effects on ventricular repolarization by improving the prolonged QT duration in rats with metabolic syndrome and this effect was generated by the KCNQ and KCNH2 gene families.

Keywords Melatonin · Metabolic syndrome · Fructose · Cardiac ions channels · QTc

Introduction

Metabolic syndrome refers to a cluster of metabolic abnormalities such as insulin resistance, dyslipidemia, abdominal obesity, hyperglycemia and increased blood pressure [1]. The consumption of fructose is increasing in modern societies and it is used in many foodstuffs. In addition, the consumption of foods and beverages produced with fructose obtained from corn holds an essential place in modern societies [2]. It is also known that high amount of fructose consumption causes metabolic syndrome. In recent years, it’s reported that metabolic syndrome may cause impaired ventricular repolarization, atrial fibrillation, and supraventricular or ventricular arrhythmias in the heart [3].

The endogenous circadian timing regulating system placed in the suprachiasmatic nucleus (SCN) optimally regulates most of human physiology across the 24-h day. Disruption in circadian rhythm follows lifestyle changes such as overnutrition at night. Therefore, increased risk of hypertension, impaired glucose intake into the muscles, high insulin secretion, increasing in abdominal fat, fatty liver, obesity, diabetes, and cardiovascular diseases have been observed.
in several studies [4, 5]. On the other hand, association is reported between disrupted physiological rhythm and suppression in melatonin secretion which is an endogenously produced molecule by epidemiological and experimental studies. It has been reported that decreasing in melatonin secretion due to the disruption of circadian rhythm in people with metabolic syndrome surprisingly cause increased tendency to heart attack and/or arrhythmia. [6].

Voltage-gated K⁺ ion channels have essential status on the functional activity of cardiac myocytes, as well as neurons, epithelial and smooth muscle cells [7]. It is known that Kv7.1–5 channels, which are Kv7 channel subtypes, are expressed in the left and right ventricles of the heart and responsible from the slowly activating delayed rectifier K⁺ ion current (IKs) in the heart. Kv7 channels (Kv7.1–5) are encoded by the KCNQ gene family (KCNQ1–5) [8]. A review of recent findings reveals that there is a strong association between Kv7 channel functions and cardiovascular risk factors including diabetes, hypertension and obesity, which are also the parameters of the metabolic syndrome. In addition, Kv7 channels may defined as molecular targets for the prevention and treatment of metabolic syndrome [9]. For instance, dysfunctions in the KCNQ1 gene lead to increase in the risk of developing type 2 diabetes in the future and impairment in pancreatic β cell function [10].

As another ion channel, Kv11.1 greatly contributes to the electrical activity of the heart in the phase 3 (repolarization phase) of the formation of cardiac action potential and it is encoded by the KCNH2 or hERG gene (human ether-à-go-go-related gene). The KCNH2 gene encodes the fast outwardly delayed rectifier K⁺ ion current (IKr) and it is encoded by the KCNH2 or hERG gene (human ether-à-go-go-related gene). The KCNH2 gene encodes the fast outwardly delayed rectifier K⁺ ion current (IKr), and mutations in the KCNH2 gene or external interventions with drugs cause prolongation of ventricular repolarization with a decrease in repolarizing IKr ion current and prolongation of the QT interval in ECG [11].

In the metabolic syndrome model that we applied in this study, it was mainly aimed to examine the expression levels of genes encoding Kv7 and Kv11.1 channels and in relation to this, the possible alterations in QT duration in ECG. In addition, it was aimed to present the effects of melatonin on metabolic syndrome by investigating aforementioned genes encoding cardiac K⁺ ion channels. We suppose that revealing the effects of melatonin on K⁺ ion channels in heart is very essential in understanding the mechanisms of cardiac ventricular arrhythmias that occurs in metabolic syndrome.

### Materials and methods

#### Experimental animals

In this study, 32 Sprague Dawley rats (3 months) were obtained from the Experimental Animals Center of Trakya University. The study was conducted after obtaining the approval from the Trakya University Experimental Animals Local Ethics Committee (approval number: TUHADYEK: 2019.01.01). All animals were fed ad libitum and housed at standart laboratory conditions (temperature: 22 ± 2°C; humidity: 50–55%; light/dark cycle: 12/12 h).

#### Study design

The groups are designed as follows

Control (C) Group (n = 8): The rats in this group were fed with standard diet + drinking water. Feeding duration lasted for 8 weeks in total. All rats in this group were given vehicle to dissolve melatonin during the last two weeks by oral gavage between 09:00–10:00 am in the morning.

Melatonin (MEL) Group (n = 8): The rats in this group were fed with a standard diet + drinking water for 8 weeks. In the last two weeks of the feeding process, freshly prepared daily melatonin (20 mg/kg/day, absolute GR for analysis, Cas-No-73–31-4, MERCK) was administered via oral gavage between 09:00–10:00am in the morning [12].

Metabolic Syndrome (MS) Group (n = 8): The rats in this group were fed with standard diet and freshly prepared daily fructose (200 g/L) was added into the drinking water for 8 weeks [13]. All rats were given vehicle to dissolve melatonin by oral gavage between 09:00–10:00am for the last two weeks.

Metabolic Syndrome + Melatonin (MS + MEL) Group (n = 8): The rats in this group were fed with standard diet and freshly prepared daily fructose (200 g/L) was added into the drinking water for 8 weeks. In the last two weeks of the feeding period, freshly prepared melatonin (20 mg/kg/day) was administered to the rats by oral gavage between 09:00–10:00am in the morning.

#### Metabolic syndrome model

Daily freshly prepared D-fructose (Sigma-Aldrich, CatNo: F0127-5 KG) was added to the drinking water of a total of 16 rats in the MS and MS + MEL groups at dose of 200 g/L [13]. Considering the daily water consumption of the rats, their drinking water was daily checked. After the fructose treatment, all rats’ glucose, insulin resistance, triglyceride, total cholesterol and LDL-C levels were analyzed.

#### Blood pressure measuring and electrocardiography (ECG) recording

Systolic blood pressure, diastolic blood pressure and mean arterial pressure measurements of all rats were recorded from the tail artery (tail-cuff plethysmography method) in
order to determine the change in blood pressure which is one of the essential marker of metabolic syndrome. Before the blood pressure measuring the rats were let to get familiar to the method for 5 min. Blood pressure measurements were performed in all rats regularly for 3 different times: the first day, the 6th week and the 8th week of the study.

In the metabolic syndrome model that we applied in our study, ECG recordings were taken immediately after blood pressure measurements by using extremity derivations under sedation anesthesia (ECG device: 35 Hz; Poly-Spectrum 12 channel ECG-System, Poly-Spectrum-8, Neurosoft, 5, Voronin str., Ivanovo, Russia). The corrected QT values were calculated according to Bazett’s Formula (QTcB) as follow; QTcB = QT/√RR. Statistical analyses of QTcB were conducted by computing the mean of three consecutive heartbeats on ECG records [14].

Heart tissue harvesting and biochemical analysis

At the end of the 8th week of the study, following the intra-cardiac blood collection, hearts were removed under general anesthesia (5 mg/kg xylazine, Rompun®, Bayer, Istanbul, Turkey and 60 mg/kg ketamine hydrochloride, Ketalar®, Eczacibasi, Istanbul, Turkey). Left ventricular tissue samples were isolated from the extracted hearts and transferred into DNase-RNase free cryogenic tubes and placed in deep freezer at −80 °C until the genetic analyses. Afterwards, the gene expression study from all left ventricular samples was performed by using quantitative Real-Time PCR method (The Applied Biosystems StepOne Real-Time PCR). Insulin, glucose, HOMA-IR (Homeostasis Model Assessment Index), triglyceride, total cholesterol, and LDL levels were determined in the serum samples. Glucose, triglyceride, total cholesterol, and LDL levels were determined by using standard methods on an autoanalyzer (Abbot Architect c16, USA). HOMA-IR index was used to evaluate insulin resistance. Insulin level in serum samples obtained from cardiac blood was evaluated by ELISA method (BT LAB Cat. No: E0707Ra).

Gene expression analysis of potassium ion channels in the left ventricle

At the end of the experimental period, left ventricle tissue samples were harvested from all rats in each group and homogenized (RETSCH, MM 400). After that, total RNA was isolated from left ventricle tissue homogenates by using a QIAamp RNA spin column protocol (Ambion Pure Link RNA Mini-Kit). The total RNA’s quality and amount were evaluated by using NanoDrop ND-1000 Spectrophotometer under 260/280 absorbance ratio and the RNA concentrations of the samples were equalized. Reverse transcription was performed manually by applying the kit protocol (High Capacity cDNA Reverse Transcription Kit, 200 reaction, USA). Synthesized cDNA samples were used for quantitative Real-Time PCR (qRT-PCR) study (The Applied Biosystems®, 2720 Thermal Cycler). Gene expression levels were analyzed by using Taqman Probe. Gene expressions were determined via the relative fold change with respect to the control group and normalized with β-actin as housekeeping gene. The comparative cycle threshold method ($2^{-\Delta\Delta C_T}$) was used to analyze the expression levels of the mRNAs. Primer ID numbers of Kcnq1, Kcnq3, Kcnh2 and β-actin were Rn00583376_m1, Rn00580995_m1, Rn01442522_m1, Rn00667869_m1, respectively (Thermo Fisher Scientific).

Statistical analysis

The data were analyzed with SPSS Package Program version 20.0 (License No: 10240642). Mean and standard deviations were used in the presentation of the data. The compliance of the variables to the normal distribution was evaluated. One-Way ANOVA and Kruskal Wallis Test was used to compare variables. In cases of significance between the groups, Mann Whitney U test with Bonferroni correction was applied (p < 0.05 was considered as statistically significant).

Results

Biochemical parameters of the metabolic syndrome model

At the end of the experimental process, biochemical analyses were performed on serum samples obtained from all rats’ blood. As a result of the statistical evaluations, it was found that insulin, glucose, HOMA-IR, total cholesterol, and LDL values were significantly changed (Table 1). The insulin data of all groups were compared and it was observed that the insulin values of the MS group were significantly increased compared to the C group, and that there was a significant decrease in the MS + MEL group compared to the MS group as a result of melatonin treatment (p < 0.05). In addition, glucose values of the MS group increased at a statistically significant level compared to the C group and the MEL group (p < 0.05). The HOMA-IR data represents the insulin resistance value, it was seen that melatonin treatment in the MS + MEL group caused a significant reduction that was significantly increased in MS group (p < 0.001). Metabolic syndrome model induced significant elevation in total cholesterol data compared to the C group and melatonin significantly reduced this elevation (p < 0.05). Therewithal, LDL was significantly increased in MS group and it was significantly reduced in MS + MEL group after melatonin administration (p < 0.001).
Blood pressure values

The hypertension was observed at the sixth week of the study according to the systolic blood pressure values of the rats in MS group. However, the increased systolic blood pressure was significantly reduced after melatonin treatment in MS + MEL group compared to MS group (p < 0.001) (Table 2). The significant elevation in diastolic blood pressure compared to group C was observed at 8th week and melatonin significantly reduced this increase in MS + MEL group (p < 0.001) (Table 3). The significant increase was firstly observed at 6th week for mean arterial pressure in MS group compared to group C (123.7 ± 4.0 vs 115.0 ± 8.8, respectively, p < 0.001). On the other hand, melatonin could significantly reduce this elevation in MS + MEL group at 8th week of the study compared to MS group (110.8 ± 5.3 vs 128.2 ± 3.4, respectively, p < 0.001).

Table 1: Comparison of biochemical parameters of the groups

| Groups          | C (n = 8) (m ± sd) | MEL (n = 8) (m ± sd) | MS (n = 8) (m ± sd) | MS + MEL (n = 8) (m ± sd) |
|-----------------|--------------------|----------------------|--------------------|-------------------------|
| Insulin (mlU/L) | 4.9 ± 0.1          | 5.4 ± 0.5            | 6.1 ± 1.4^a        | 4.6 ± 0.3^c             |
| Glucose (mg/dl) | 188.8 ± 38.8       | 178.8 ± 12.4         | 259.0 ± 64.5^a,b   | 216.7 ± 39.7            |
| HOMA-IR         | 3.7 ± 0.6          | 3.8 ± 0.3            | 6.1 ± 1.3^b        | 4.0 ± 0.8^c             |
| Triglyceride (mg/dl) | 33.8 ± 6.2     | 36.7 ± 8.2           | 54.2 ± 19.7        | 38.2 ± 4.2              |
| Total Cholesterol (mg/dl) | 56.0 ± 11.4     | 54.7 ± 9.9           | 79.6 ± 66.6^a,b    | 74.1 ± 37.0^c           |
| LDL (mg/dl)     | 16.8 ± 4.3         | 18.1 ± 4.3           | 28.7 ± 2.0^a,b     | 22.0 ± 1.5^c            |

C: Control, MEL: Melatonin, MS: Metabolic syndrome, MS + MEL: Metabolic syndrome + melatonin. Data are presented as mean ± standard deviation (m ± sd)

^a Compared to C group, p < 0.05
^b Compared to MEL group, p < 0.05
^c Compared to MS group, p < 0.05

Table 2: Systolic blood pressure values of all groups

| Groups          | 1st day (m ± sd) | 6th wk (m ± sd) | 8th wk (m ± sd) |
|-----------------|------------------|-----------------|-----------------|
| C (n = 8)       | 123.7 ± 5.9      | 126.0 ± 4.5     | 124.1 ± 3.4     |
| MEL (n = 8)     | 123.7 ± 6.4      | 128.6 ± 2.2     | 125.9 ± 3.8     |
| MS (n = 8)      | 125.5 ± 3.1      | 147.1 ± 6.3^a,b | 152.4 ± 4.1^a,b |
| MS + MEL (n = 8)| 128.6 ± 1.5      | 136.2 ± 4.3     | 124.1 ± 5.2^c   |

C: Control, MEL: Melatonin, MS: Metabolic syndrome, MS + MEL: Metabolic syndrome + melatonin. All results are presented as mean ± standard deviation (m ± sd) for eight rats in each group

^a Compared to C group, p < 0.001
^b Compared to MEL group, p < 0.001
^c Compared to MS group, p < 0.001

Table 3: Diastolic blood pressure values of all groups

| Groups          | 1st day (m ± sd) | 6th wk (m ± sd) | 8th wk (m ± sd) |
|-----------------|------------------|-----------------|-----------------|
| C (n = 8)       | 99.8 ± 8.6       | 110.3 ± 10.1    | 97.1 ± 5.2      |
| MEL (n = 8)     | 98.2 ± 7.05      | 106.0 ± 3.2     | 101.7 ± 4.4     |
| MS (n = 8)      | 106.5 ± 5.8      | 112.0 ± 5.6     | 116.0 ± 5.0^b   |
| MS + MEL (n = 8)| 107.3 ± 3.2      | 109.7 ± 2.9     | 100.7 ± 4.6^c   |

C: Control, MEL: Melatonin, MS: Metabolic syndrome, MS + MEL: Metabolic syndrome + melatonin. All results are presented as mean ± standard deviation for eight rats in each group

^a Compared to C group, p < 0.001
^b Compared to MEL group, p < 0.001
^c Compared to MS group, p < 0.001

Electrocardiographic evaluations

ECG recordings were applied on three different times during the study (1st day, 6th week and 8th week). There was no significant change in corrected QT on the first day and the sixth week recordings. On the other hand, we observed statistically significant alterations on the week eight. The significant prolongation on QT interval for MS group was recorded according to Bazett’s formula (QTcB) compared to C and MEL groups (p < 0.001). However, melatonin treatment on MS + MEL group significantly reduced the prolongation observed in MS group (p < 0.001) (Fig. 1).

Gene expression analyses

The relative fold changes of left ventricular KCNQ1 gene mRNA expression of all groups were compared and it’s
concluded that mRNA expression of the KCNQ1 gene was significantly reduced with metabolic syndrome compared to C and MEL groups (p < 0.005, p < 0.001, respectively). On the other hand, melatonin treatment to the rats with metabolic syndrome (MS + MEL group) significantly increased the KCNQ1 gene expression values (p < 0.05) in comparison to MS group (Fig. 2A). KCNQ3 gene expression were significantly reduced for all groups compared to control (p < 0.05) (Fig. 2B). Melatonin administration in metabolic syndrome did not cause any significant alteration in the expression of the KCNQ3 gene.

KCNH2 gene expression level was significantly increased for MS group compared to C and MEL groups (p < 0.001). This increase in MS group was significantly reduced after melatonin treatment in MS + MEL group (p < 0.05) (Fig. 2C).

Discussion

In developing countries, disruptions occur in the circadian rhythm with the changing lifestyle. This situation poses a great risk in terms of obesity, type 2 diabetes and cardiovascular diseases that the prevalence of which is gradually increasing [4]. On the other hand, circadian rhythm disturbances disrupt the autonomic nervous system functions in a way that predominates sympathetic activity, and as a result, high blood pressure, impaired glucose utilization in muscles, increased insulin secretion, fatty liver and abdominal steatosis may be observed [15]. The effects of melatonin were investigated in the present study because of the similarity of the symptoms above mentioned related to circadian rhythm disturbances with the symptoms of metabolic syndrome. Human genome studies indicate a relation between circadian rhythm regulation, melatonin synthesis and glucose homeostasis [16, 17]. Studies also reveal a decrease in plasma melatonin level in the etiology of type 2 diabetes and metabolic syndrome [18, 19]. Low melatonin levels are associated with the risk of many cardiac diseases such as coronary heart disease, left ventricular hypertrophy, infarction, and congestive heart failure [20, 21].

The alterations of genes encoding cardiac K+ ion channels may cause cardiac electrical remodeling. Therefore, the action potential duration varies depending on the cardiac K+ ion density, and these channels became an important target
for the correction of supraventricular arrhythmias [22]. Determining how melatonin plays essential role in protection against cardiovascular diseases and affects the expressions of genes encoding cardiac K+ ion channels in metabolic syndrome seems to be important in terms of elucidating the relationship between metabolic syndrome-cardiac K+ ion flow and melatonin. In our study, we determined that mRNA expression levels of KCNQ genes were decreased with metabolic syndrome. However, we observed that KCNH2 gene expression level was not decreased in rats with metabolic syndrome. Thus, the current research revealed that K+ ion channels have not altered in the same manner with metabolic syndrome.

Melatonin has significantly decreased the hyperglycemia, insulin resistance, dyslipidemia and hypertension that are the essential markers of the metabolic syndrome. In addition, ECG recordings revealed a prolongation in the QT duration as a result of metabolic syndrome, and this prolongation significantly decreased to the values close to those in the control group with the melatonin treatment. We have also observed that statistically significant alterations on the KCNQ1 and KCNH2 genes supports the prolongation of the QT duration, which is an important parameter of ventricular repolarization.

It has been interpreted that inhibitors of the Kv11.1 (hERG) channel encoded by the KCNH2 gene and cellular mediators limiting the open time these channels may improve the susceptibility to supraventricular arrhythmias in patients with metabolic disorders by modulation of the action potential duration [21, 22]. It has been also reported that increasing in the density of the K+ ion channel (Kv11.1) flow makes guinea pigs more susceptible to supraventricular arrhythmias in metabolic syndrome [22]. In our study, we determined that the expression of the KCNH2 gene encoding the Kv11.1 channel significantly increased in rats subjected to fructose induced metabolic syndrome.
syndrome model, and melatonin treatment caused a significant reduction in this increment. Therefore, the increase in the expression of KCNH2 gene in rats with metabolic syndrome may enhance the risk of supraventricular arrhythmia in these rats. In addition, considering the expression data, the fact that melatonin also acts in a corrective sense for this situation brings to mind the usability of melatonin as an effective agent in this aspect and suggests that this issue should be evaluated in more detail.

The functional contribution of fast K⁺ ion channels to arrhythmias associated with metabolic disorders has not been fully elucidated. The prolongation of QT duration observed in ECG recordings is defined as Long QT (LQT) syndrome. The LQT syndrome may be mainly classified as LQT1 and LQT2 syndromes according to the activities of effective channels during cardiac contraction.

Disruptions in the activity of the Kv11.1 channel causing LQT2 syndrome constitute approximately ~40% of congenital LQTS cases. On the other hand, disruptions in the activity of the Kv7 channel that cause LQT1 constitute approximately 50% of the LQTS cases [23]. As a result of enhanced sympathetic activity, it is observed that the expression of the K⁺ ion channel fast component (Kv11.1) increases in order to elevate heart rate and normalize the heart rhythm with the action potential duration [24]. This is compatible with the increased expression of the Kv11.1 gene in our study. The ECG data we obtained in our study reveal that the QT durations are prolonged in rats with metabolic syndrome. It was determined that melatonin had significantly decreasing effect on the prolonged QT duration. We conclude that the prolonged QT interval observed in the ECG records of the rats with metabolic syndrome developed due to the disrupted Kv7
channel activity rather than the Kv11.1 channel disruption. We also suppose that the decrease in Kv7 channel expression, which is responsible for approximately 50% of LQT syndromes, has more essential and effective role in this aspect than the Kv11.1 channel in the ventricular action potential repolarization phase.

The present study was primarily focused on the interaction and relation between metabolic syndrome and alterations of cardiac K+ ion channels’ gene expression after melatonin treatment. In rats for which the metabolic syndrome model was applied, it was determined that melatonin a) had ameliorative effects on the components of metabolic syndrome, b) improved the prolonged QT duration in ECG, c) normalized the expressions of the KCNQ1 and KCNH2 genes encoding cardiac K+ ion channels in the fructose-induced metabolic syndrome rat model (hypothetically illustrated in Fig. 3).

Conclusion

All these outcomes define that melatonin has an ameliorative effect on both blood parameters and hemodynamic data in metabolic syndrome. In addition, melatonin may play an effective cardioprotective role through K+ ion channels in cardiovascular diseases developed with metabolic syndrome. In our study, we thought that evaluating the relationship between metabolic syndrome, melatonin and cardiac ion channels may guide the return of metabolic syndrome parameters to healthy levels. According to the findings, the expressions of KCNQ and KCNH2 genes differ from each other in metabolic syndrome. It was determined that melatonin had an ameliorative effect on ventricular repolarization by shortening the prolonged QT duration in rats with metabolic syndrome, and this effect was generated by the KCNH2 and KCNQ gene family. The findings of the present study will provide insight into the studies conducted for the amelioration of the impairments in cardiac parameters observed in metabolic syndrome.

Author contributions MAO and SAV conceived and designed the research. MAO and SAV conducted the animal experiments. ROO and MAO performed the laboratory analysis. SAV and MAO wrote the manuscript. All authors read and approved the manuscript.

Funding This study was supported by the foundation of TUBAP (Scientific Research Projects Office of Trakya University, Project number: TUBAP 2018/291) and summarised from PhD Thesis of the Corresponding Author.

Conflict of interest No potential conflict of interests were reported by the authors.

Ethical approval This study was approved by the Trakya University Experimental Animals Local Ethics Committee in accordance with ethical guidelines for the Care and Use of Laboratory Animals (approval number: TUHADYEK: 2019.01.01).

References

1. Lehnen AM, Rodrigues B, Irigoyen MC, De Angelis K, Schaan BDA (2013) Cardiovascular changes in animal models of metabolic syndrome. J Diabetes Res 2013:e761314
2. Tappy L, Lé KA (2010) Metabolic effects of fructose and the worldwide increase in obesity. Physiol Rev 90(1):23–46
3. Aromolaran AS, Boutjdir M (2017) Cardiac ion channel regulation in obesity and the metabolic syndrome: relevance to long QT syndrome and atrial fibrillation. Front Physiol 8:431
4. Scheer FA, Hilton MF, Mantzoros CS, Shea SA (2009) Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci USA 106:4453–4458
5. Bixler E (2009) Sleep and society: an epidemiological perspective. Sleep Med 10(suppl1):S3–S6
6. Reiter RJ, Tan DX, Korkmaz A, Ma S (2012) Obesity and metabolic syndrome: association with chronodisruption, sleep deprivation, and melatonin suppression. Ann Med 44(6):564–577
7. Barrese V, Stott JB, Greenwood IA (2018) KCNQ-encoded potassium channels as therapeutic targets. Annu Rev Pharmacol Toxicol 58:625–648
8. Hedegaard ER, Johnsen J, Povlsen JA, Jespersen NR, Shammuganathan JA, Laursen MR et al (2016) Inhibition of Kv7 channels protects the rat heart against myocardial ischemia and reperfusion injury. J Pharmacol Exp Ther 357:94–102
9. Fosmo AL, Skraastad OB (2017) The Kv7 channel and cardiovascular risk factors. Front Cardiovasc Med 4:75
10. Jonsson A, Isomaa B, Tuomi T, Taneera J, Salehi A, Nilsson P et al (2009) A variant in the KCNQ1 gene predicts future type 2 diabetes and mediates impaired insulin secretion. Diabetes 58(10):2409–2413
11. January CT, Gong Q, Zhou Z (2000) Long QT syndrome: cellular basis and arrhythmia mechanism in LQT2. J Cardiovasc Electrophysiol 11:1413–1418
12. Demirtas CY, Pasaoğlu OT, Birçan FS, Kantar S, Turkozkan N (2015) The investigation of melatonin effect on liver antioxidant and oxidant levels in fructose-mediated metabolic syndrome model. Eur Rev Med Pharmacol Sci 19(10):1915–1921
13. Yılmaz Demirtas C, Birçan FS, Pasaoğlu OT, Turkozkan N (2018) The effects of resveratrol on hepatic oxidative stress in metabolic syndrome model induced by high fructose diet. Brasile Lek Listy 119(1):36–40
14. Ovali MA, Uzun M (2017) The effects of melatonin administration on KCNQ and KCNH2 gene expressions and QTc interval in pinealectomised rats. Cell Mol Biol (Noisy-le-grand) 63(3):45–50
15. Buïjs RM, Scheer FA, Kreier F, Yi C, Bos N, Goncharuk VD et al (2006) Organization of circadian functions: interaction with the body. Prog Brain Res 153:341–360
16. Bouatia-Naji N, Bonnefond A, Cavadic-Proenca C, Sparso T, Holmkvist J, Marchand M et al (2009) A variant near MTNR1B is associated with increased fasting plasmaglucose levels and type 2 diabetes risk. Nat Genet 41(1):89–94
17. Bonnefond A, Clement N, Fawcett K, Yengo L, Vaillant E, Guillaume JL et al (2012) Rare MTNR1B variants impairing melatonin receptor 1B function contribute to type 2 diabetes. Nat Genet 44(3):297–301
18. Mäntele S, Otway DT, Middleton B, Bretschneider S, Wright J, Robertson MD et al (2012) Daily rhythms of plasma melatonin, but not plasma leptin or leptin mRNA, vary between lean, obese and type 2 diabetic men. PLoS ONE 7(5):e37123

19. Corbalán-Tutau D, Madrid JA, Nicolás F, Garaulet M (2014) Daily profile in two circadian markers “melatonin and cortisol” and associations with metabolic syndrome components. Physiol Behav 123:231–235

20. Su H, Chen T, Li J et al (2017) Correlations of serum cyclophilin a and melatonin concentrations with hypertension-induced left ventricular hypertrophy. Arch Med Res 48:526–534

21. Dominguez-Rodriguez A, Abreu-Gonzalez P, Piccolo R, Galasso G, Reiter RJ (2016) Melatonin is associated with reverse remodeling after cardiac resynchronization therapy in patients with heart failure and ventricular dyssynchrony. Int J Cardiol 221:359–363

22. Martinez-Mateu L, Saiz J, Aromolaran AS (2019) Differential modulation of ik and ica, l channels in high-fat diet-induced obese guinea pig atria. Front Physiol 10:1212

23. Tester DJ, Will ML, Haglund CM, Ackerman MJ (2005) Compendium of cardiac channel mutations in 541 consecutive unrelated patients referred for long QT syndrome genetic testing. Heart Rhythm 5:507–517

24. Schwartz PJ, Priori SG, Spazzolini C et al (2001) Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation 103:89–95

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