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Original Article

Protective effect of agomelatine on some cardiovascular and metabolic parameters in experimentally induced type 2 diabetes mellitus in rats

Pharmacology

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ABSTRACT

Background: Diabetic individuals have a higher incidence of depression compared to the general population, and it is a significant risk factor for cardiovascular complications in those patients. In turn, depression and type 2 diabetes mellitus (T2DM), as well as its macrovascular complications, have a reciprocal relationship. Agomelatine, an atypical antidepressant, has been shown to have anti-inflammatory and antioxidant activities. It is a melatonin receptor agonist and a serotonin receptor antagonist.

Objective: To demonstrate the protective effects of agomelatine on cardiovascular and hyperglycemic disorders.

Methodology eighteen adult male albino rats were included in the study and assigned into three groups: Group I: Considered as control group, Group IIa: Diabetic (non-treated) group where diabetes was induced by 20%weight/volume (W/V) fructose sweetened water for 14 days followed by intraperitoneal injection of alloxan at a dosage of 150 mg/kg, Group IIb: Diabetic agomelatine treated group; received agomelatine (20 mg/kg/day) for four consecutive weeks. Blood pressure and electrocardiogram (ECG) measurements were performed. Blood samples were collected for measuring of tumor necrosis factor-alpha level, blood glucose level, glycated hemoglobin, and serum insulin in the end of experimental period. Additionally, the histopathological examination for aortic and heart tissues was performed.

Results: Agomelatine produced a significant ($p< 0.001$) decreased systolic, diastolic and mean arterial blood pressure and improved ECG abnormalities. The same treatment caused a significant ($P<0.001$) decrease in tumor necrosis factor-alpha (TNF-α) level, blood glucose level, glycated hemoglobin, and improvement of insulin resistance, in addition to a significant increase in serum insulin level. Histopathological changes in myocardial and aortic tissues were also improved by agomelatine.

Conclusion: Agomelatine has a cardio-protective effect against cardiovascular abnormalities in the diabetic rats that may be mediated by improvement of glucose hemostasis, restoration of hemodynamics (blood pressure and ECG), increased nitric oxide (NO) bioavailability, and alleviation of inflammation.

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INTRODUCTION

Diabetes Mellitus (DM) is considered as a chronic metabolic disease characterized by not only insulin resistance and hyperglycemia but also cognitive impairment [1]. Cardiovascular diseases (CVDs) are the most prevalent and serious consequences of type 2 diabetes mellitus (T2DM). Adults with diabetes are more likely to develop heart disease or a stroke than those who do not have diabetes, with a likelihood that is 2-4 times higher [2,3]. The risk of T2DM macrovascular complications is increased by depression. Additionally, higher incidence of depression can also result from diabetes' macrovascular problems [4]. The precise manner in which depression influences the probability of cardiovascular disease in patients with T2DM is unclear. Presently, it is believe that this association is related to neuroendocrine dysfunctions and inflammatory processes

affecting the vascular endothelium, and these mechanisms are more interconnected than isolated [5,6].

The over-activity of the hypothalamic-pituitary-adrenal axis during depression results in excessive secretion of cortisol, which in turn causes damage of vascular endothelial cell and insulin resistance. Poor medication adherence and an unhealthy lifestyle make depression patients more susceptible to hyperglycemia, which encourages coagulopathy and fibrinolysis. Atherosclerosis and cardiovascular disease, endothelial dysfunction, inflammation, and aberrant coagulation are all known to be accelerated by diabetes-induced hyperglycemia and insulin resistance[7].

Agomelatine is a synthetic analogue of the natural hormone melatonin and an atypical antidepressant. It acts as agonist on melatonin receptors (MT1 and MT2)and as an antagonist on serotonin receptors (5-HT2C and 5-HT2B)[8]. Agomelatine has a longer half-life and a higher binding affinity for MT1 and MT2 receptors than melatonin [9]. It also has a relatively favorable side effects profile, and its therapeutic benefits are similar with that of the other anti-depressant drugs. Unlike other anti-depressants, agomelatine does not cause weight gain, metabolic abnormalities, sexual dysfunction or withdrawal symptoms [10,11]. According to Tain et al. [12] and Khalaf et al. [13], Agomelatine therapy had been found to prevent programmable hypertension and to have a cardioprotective effect against myocardial injury. Agomelatine has been proposed as a potentially effective treatment option for depression and anxiety symptoms, as well as for neuropathic pain associated with DM, based on promising results from clinical and preclinical studies[14,15]. In recent study, pretreatment with agomelatine reduces the development of hyperglycemia and hypoinsulinemia in mice with DM induced by streptozotocin [16].

Depending on those previous studies, the current study aimed to evaluate agomelatine's protective effects on cardiovascular and hyperglycemic disorders.

MATERIALS AND METHODS

Drugs and chemicals

Agomelatine – Gifted from "Mash premiere for pharma-ceutical industries, Egypt". It was supplied in the form of white powder, and was freshly prepared daily in distilled water. Alloxan monohydrate – (Sigma Aldriach Company, St Lous Mo, USA): Supplied in the form of pink crystalline powder which was dissolved in cold normal saline (0.9%) forming fresh solution of concentration of 2%. Fructose - Piochem for laboratory chemicals, Egypt: Supplied as white powder and dissolved in drinking water and provided to animals as a concentration of 20%weight/volume.

Experimental design

Eighteen adult male albino rats with body weight 220–240 gram, were purchased from AL Nile Animal Farm in Cairo, Egypt. After a week of acclimatization, the rats were housed in a well-controlled, 12-hour light/dark cycle environment. They were given their standard pellet chow during the day, with temperatures and humidity kept between 25–27°C and 52–57%, respectively. The rats were divided into three groups (six rats in each group) including, Group I (control group) that received only food and water; Group IIa, a diabetic non-treated group, in which DM was induced by fructose/alloxan model and then administered saline solution; Group IIb, a diabetic agomelatine treated group in which diabetic rats were administered agomelatine (20 mg/kg/day) orally by oral gavage for four weeks [17].

Induction of diabetes: before induction of diabetes, checking blood glucose to obtain the baseline blood glucose level. Diabetes was induced as described by Fabiyi, Edebor and Fasanmade [18]; rats were administered 20%w/v fructose sweetened water for 14 days followed by intraperitoneal injection of alloxan (150mg/kg) on the 15th day. The diabetic animals were continuously monitored for seven consecutive days after being administered alloxan, and on day eight of the alloxan injection, which was also the first day of treatment for the diabetic-agomelatine treated group, only diabetic rats with a fasting blood glucose level of ≥ 200 mg/dl were chosen for the present study[19]. Thereafter, blood glucose levels were checked weekly in order to observe the hyperglycemic status and also to examine the effects of agomelatine on alloxanized hyperglycemic rats.

Ethical considerations

All experimental procedures were approved by the Research Ethics Committee of the Faculty of Medicine for Girls at Al-Azhar University (Ethical approval No.671) and executed in accordance with the National Institutes of Health's Guide for the Care and Use of Laboratory Animals.

Arterial blood pressure (ABP) and ECG

Rats were fasted overnight for 6–8 hours, anaesthetized with urethane (1200 mg/kg I.P). Following examination of animal's reflexes, it was placed on a flat movable surface. After administrating anesthesia, the skin on the ventral side of the neck is cleaned and shaved. Small incision of 1.5-2 cm was performed in the neck in order to cannulate the carotid artery and perform a tracheostomy. Sterile polyethylene (PE) tubing and a 26 G×1/2½ needle pre-filled with heparinized normal saline (0.5 IU/ml) were used to cannulate the blood vessel. The cannulated blood vessel was then connected to a pressure transducer and power Lab 4/35 hardware and power Lab Chart pro software (AD Instruments, Australia) to measure blood pressure. For recording ECG; reference, positive, and

negative subcutaneous ECG electrodes were placed in the left thigh, left foreleg, and right foreleg respectively [20].

Collection of blood samples

From cannula inserted in the carotid artery, blood samples were collected. Blood was divided into two aliquots; one was anti-coagulated for HbA1c assessment, which was analyzed freshly and the other for serum separation was left to clot at room temperature for 30 minutes. Then the sera were separated by centrifuging them for 20 minutes at 3,000 rpm. After that, samples were kept at -20 °C for biochemical examination [21].

Biochemical analysis

Fasting serum glucose level was estimated according to the method of Trinder [22] using Glucose Colorimetric PAP assay kit (Greiner Diagnostic GmbH., Germany). Fasting serum insulin was measured using a commercial rat insulin ELISA kits. Glycated hemoglobin was carried out by the method of Beisswenger et al.[23], and the values of homeostasis model assessment of insulin resistance (HOMA-IR) were calculated using the following equation: HOMA-IR = fasting serum insulin (ng/ml) x fasting serum glucose (mg/dl) / 405 [24].The level of tumor necrosis factor-alpha (TNF-α) was determined using commercially available ELISA kits (Quansys Biosciences, Logan, UT, USA) following the manufacturer's protocols.

Histopathological study

After the heart and aorta were stored in 10% formalin solution, dried with absolute alcohol, cleaned with xylene, the sections were cut at 5 µm on a rotatory microtome, then stained with hematoxylin and eosin (H&E) for histopathological examination by a light-microscope.

Statistical analysis

Data expressed as mean ± standard deviation. The one-way analysis of variance (ANOVA) was used, followed by the post hoc Tukey test to determine the statistical significance of the differences between the groups. A p-value <0.05 was considered significant.

RESULTS

Arterial blood pressure (ABP)

Table (1) demonstrates higher systolic, diastolic and mean arterial blood pressure (MAP) in the diabetic group (p 0.001) as compared to the control group. Agomelatine treatment significantly decreased arterial blood pressure (systolic, diastolic, and mean arterial blood pressure).

Regarding ECG as shown in Table (2), diabetes produced a significant ($p < 0.05$) decrease in heart rate associated with prolonged QT interval when compared to the control group. Using agomelatine significantly normalized the ECG abnormalities.

Biochemical study

The study revealed that there was a significant rise in fasting blood glucose levels, HbA1c, HOMA-IR and TNF-α ($p < 0.001$) in non-treated diabetic rats compared to the control group. However, these values improved upon treatment with agomelatine as shown in **Table (3).** Additionally, diabetic rats had a significantly lower serum insulin level ($p < 0.001$) compared to the control group. Nevertheless, treatment with agomelatine (20mg/kg) led to a significant increase in serum insulin levels ($p < 0.001$) in diabetic treated rats compared to the untreated diabetic rats.

Table (1): Comparison of arterial blood pressure measurement among different experimental groups

Blood pressure (mmHg)	Experimental groups			F-test	p-value
	GI n=6	GIIa n=6	GIIb n=6		
Systole (mmHg)	105.00±9.12 c	144.67±5.09 a	131.17±4.62 b	56.130	0.001*
Diastole (mmHg)	69.33±9.61 c	116.33±10.75 a	100.00±6.36 b	41.303	0.001*
MAP (mmHg)	86.17±7.94 c	131.83±7.25 a	117.00±4.24 b	73.154	0.001*

GI: Control group, GIIa: Diabetic non-treated group, GIIb: Diabetic-agomelatine treated group, MAP: mean arterial blood pressure, *Significant p-value (<0.05). Values in each row which have different letters are significantly different: a, consider the largest value, while c, consider the lowest value.

Table (2): Comparison of heart rate (beat per minute), QT interval (second) and ST segment (millivolt) among different experimental groups

ECG parameter diabetic groups	Experimental groups			F-test	p-value
	GI n=6	GIIa n=6	GIIb n=6		
Heart Rate (BPM)	318.47±24.66 a	244.58±32.25 b	297.27±29.67 a	10.303	0.002*
QT Interval (s)	0.044±0.011 b	0.066±0.011 a	0.044±0.016 b	7.753	0.005*
ST segment (mV)	0.019±0.004	0.026±0.003	0.022±0.006	2.964	0.082

GI: Control group, GIIa: Diabetic non-treated group, GIIb: Diabetic-agomelatine treated group, BPM: beat per minute, S: second, mV: millivolt. *Significant p-value (<0.05). Values in each row which have different letters are significantly different: a, consider the largest value, while c, consider the lowest value.

Table (3): Comparison of glucose homeostasis parameters and tumor necrosis factor (TNF)-α among different experimental groups

Glucose homeostasis parameters	Experimental groups			F-test	p-value
	GI n=6	GIIa n=6	GIIb n=6		
Fasting blood glucose (mg/dl)	88.50±9.35 c	389.83±27.63 a	203.48±8.01 b	454.902	0.001*
Fasting Serum insulin (ng/ml)	2.82±0.39 a	1.98±0.15 b	3.03±0.38 a	17.742	0.001*
HgA1c%	3.62±0.30 c	8.45±0.57 a	5.53±0.38 b	190.629	0.001*
HOMA-IR	0.62±0.13 c	1.90±0.18 a	1.52±0.24 b	71.719	0.001*
TNF-α (pg/ml)	22.30±3.74c	126.73±13.79 a	45.50±17.66 b	104.954	0.001*

GI: Control group, GIIa: Diabetic non-treated group, GIIb: Diabetic -agomelatine treated group, HgA1c: Glycated hemoglobin, HOMA-IR: Homeostasis model assessment of insulin resistance, TNF-α: Tumor necrosis factor-alpha, *Significant p-value (<0.05). Values in each row which have different letters are significantly different: a, consider the largest value, while c, consider the lowest value.

Histopathological study

The microscopic examination of heart and aortic tissues is demonstrated in figure 1 and 2 respectively. Photomicrographs of a section of heart from the control group (figure 1a) showed normal cardiomyocytes, well-preserved cytoplasm with the absence of inflammatory cells and edema. Histological analysis of heart tissue in diabetic rats (figure 1b) showed distorted myocytes, disorganization of normal radiating pattern of cell plates, inflammatory cellular infiltrates, necrosis and edema. Agomelatine treated rats (figure 1c) showed improvement of heart histology including decrease inflammatory cells and nearly restore normal cardiomyocytes. The microscopic examination of aortic section from the control group (figure 2a) revealed that the intima consists of a single layer of intact endothelium. The tunica media was made up of smooth muscle and elastic fibers, while a loose connective tissue made up the adventitial outermost layer. Aortic tissue in diabetic rats (figure 2b) exhibited pathological changes, including moderate tunica media thickening, focal endothelial detachment and erosions. Agomelatine treatments (figure 2c) revealed improvement of aortic architecture.

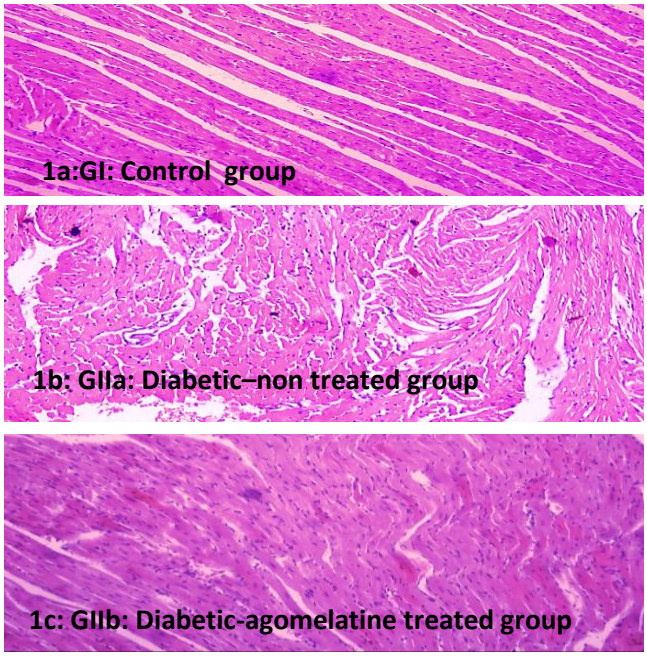

Figure (1): photomicrographs of heart tissue sections in different studied rat groups

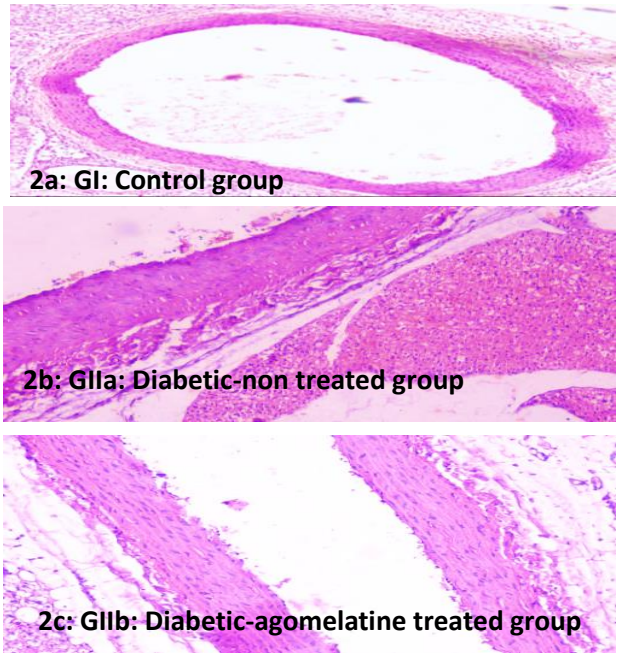

Figure (2): photomicrographs of aortic tissue sections in different studied rat groups

DISCUSSION

In the present work, the induction of T2DM was found to cause significant changes in glucose homeostasis represented by increasing fasting blood glucose (FBG) level, glycated haemoglobin (HbA1C) and the homeostasis model assessment of insulin resistance (HOMA-IR) index, while the level of fasting serum insulin was decreased. Systolic, diastolic, and mean arterial blood pressure was significantly increased. It also revealed a significant decrease in heart rate with prolongation of the QT interval when compared to control

rats. Moreover, a significant increase in TNF-α level was detected in the untreated diabetic group when compared to the control group. It is believed that type 2 diabetes mellitus is influenced by low-grade chronic inflammation [25]. TNF-α was the first pro-inflammatory cytokine to be identified as playing a role in the development of diabetes mellitus and insulin resistance. As a result, individuals with type 2 diabetes mellitus have significantly higher levels of TNF-α in their blood compared to healthy individuals[26].

In our work, compared to the diabetic untreated group, treatment with agomelatine resulted in a significant reduction in the fasting serum glucose (FSG) level, HbA1C, HOMA-IR and TNF-α in addition to an improvement in plasma insulin level. These findings are in consistent with the study carried out by Ozcan et al.[16]who reported that pretreatment of mice with agomelatine at dosage of 10 and 20 mg/kg/day significantly reduces the development of hypoinsulinemia and hyperglycemia induced by streptozotocin. Promsan et al. [27] also reported that agomelatine administration at dosage of 20 and 40 mg/kg/day, significantly reduced plasma glucose levels and improved impaired glucose tolerance in obese rats fed a high-fat diet. This effect is consistent with previous researches showed that melatonin, a hormone similar to agomelatine, modulates insulin secretion from pancreatic beta cells by interacting with melatonin receptors and stimulating the expression of phospholipase C and inositol trisphosphate (IP3). This in turn leads to the release of calcium from the endoplasmic reticulum into the cytoplasm, which can initiate insulin exocytosis and result in antihyperglycemic effects [28,29]. Moreover, it was reported that melatonin promoted pancreatic cell proliferation via activating the melatonin 2 receptor (MT2R) in vitro[30]. Agomelatine was also found to reduce weight gain, improve insulin resistance and enhance lipid and glucose metabolisms in a mouse model of obesity induced by high-fat diet. Additionally, it decreased the production of TNF-α, interleukin-1β, interleukin-6, and monocyte chemo-attractant protein-1 in liver and fat tissues, which are linked to endothelial dysfunction and obesity[31]. Diez-Echave et al. [31] added that improved glucose homeostasis and insulin sensitivity induced by agomelatine were attributed to increased glucose transporter type-4 (GLUT-4) and adenosine monophosphate activated protein kinase (AMPK) expression in fat and liver tissues, as well as increased expression of adiponectin (adipokine secreted by adipocytes)which is an anti-inflammatory and insulin-sensitizing mediator that suppresses hepatic glucose production. AMPK plays an important role in the translocation of GLUT-4 transporters to the membrane, the inhibition of liver gluconeogenesis, and the reduction of inflammation; all of these indicate the role of AMPK in insulin resistance[32].

The current study showed that induction of T2DM in rats was accompanied by a significant increase in arterial blood pressure and ECG changes including significant bradycardia with prolongation of QT interval. This aligns with an earlier investigation conducted by Fasola et al.[33]which found that rats with diabetes induced by alloxan had noticeably higher blood pressure; this was likely a symptom of a prolonged hyperglycemic state's consequences.

Hyperglycemia alters vascular structure and function by increasing vascular endothelium's production of hydrogen peroxide and lowering NO bioavailability [34,35]. Additionally, the available experimental data indicate that TNF-α is involved in the pathophysiology of hypertension. Specifically, in vitro, TNF-α promotes the generation of endothelin-1 and angiotensinogen [36]. Accordingly, the blood pressure lowering effect of agomelatine in diabetic rats in our study was attributed to its dramatic improvements in glucose hemostasis and its anti-inflammatory effects.

Our findings showed that diabetic rats exhibited a significant decrease in heart rate with prolongation of QT interval when compared to control group. This is consistent with the experimental study carried out by Oluwaseun et al. [37]who mentioned that alloxan treated rats showed significant abnormalities in ECG pattern (bradycardia with prolongation of QT interval).
It was reported that diabetes first stimulates the sympathetic nervous system, but prolonged exposure to high blood glucose level and elevated catecholamines lead to a decrease in adrenergic receptors and as a result, bradycardia may occur [38]. The prolonged QT interval has been associated with hyperglycemia, and the presence of QT abnormalities is often used as a predictor of mortality in diabetic patients [39,40].Changes in outward K+ currents are observed early after streptozotocin injection, and these changes appear to be correlated with increases in blood glucose levels and can be prevented by blocking hyperglycemia[41] . Also, it has been reported that diabetic hyperglycemia can cause pathological remodeling of the sinoatrial node (SAN), which significantly alters SAN function and decreases the velocity of SAN conduction [42]. It is possible that all these factors contributed to the ECG changes observed in our study in relation to diabetes.

Treatment with agomelatine in our study was able to restore the QT interval and heart rate remained close to values as recorded in the normal control group. These results were supported by a study carried out by Aygun and Gul [43] who demonstrated agomelatine's cardioprotective effects on doxorubicin-induced cardiotoxicity in rats by improving ECG abnormalities including QT interval, RR interval and ST segment, reducing oxidative stress and enhancing antioxidant activity.

Histopathological findings of myocardial tissues in our study showed disorganized myocardial fibers with necrosis of myocytes and infiltration of inflammatory cells in the diabetic group when compared to control group. These results are similar to the histopathological changes described by Tiss and Hamden [44]. In response to myocardial injury, inflammatory signaling is often initiated in cardiomyocytes, which involves the overproduction of reactive oxygen species (ROS) in mitochondria [45].

In our work, the serum TNF-α level was found to be significantly higher in the diabetic group, indicating an exaggerated inflammatory response and a dysregulated immune system. As demonstrated in an earlier study, pro-inflammatory cytokines directly contribute to diabetic complications and heart disease [46]. In the present study, treatment of diabetic rats with agomelatine led to a significant decrease in TNF-α level, along with the improvement of heart histology. These findings support the idea that agomelatine possesses potent anti-inflammatory properties, providing remarkable protection against diabetes-induced cardiac injury.

Beside heart, histopathological changes of aorta in the diabetic rats revealed marked intimal thickening, with features of endothelial detachment, erosion and micro-ulcerations [47,48]. Similar changes have been observed in the current study. The present findings coincide with earlier studies of Soufy et al. [49]& Shirpoor et al. [50] who found that the media thickness of the aorta increased significantly in the diabetic rats when compared to the control rats. Diabetic hyperglycemia enhances the upregulation of advanced glycation end products (AGEs) in circulating blood and tissues, which contributes to vascular complications. When AGEs engage with their receptors in the endothelial cells, reactive oxygen species (ROS) are produced and nuclear factor-κB (NF-κB) is activated. This promotes the expression of several growth factors and cytokines, which in turn induces a sustained inflammatory response[51]. Accordingly, treatment with agomelatine in our study improved aortic morphological changes due to its anti-inflammatory property.

CONCLUSION

Agomelatine has been found to have a cardioprotective effect in rats with T2DM. This effect may be attributed to an improvement in hemodynamic parameters, such as blood pressure and ECG, and glucose hemostasis, as seen by a decrease in blood glucose and insulin resistance, along with a reduction in inflammation. Therefore, it is possible that agomelatine could have positive effects on diabetes morbidity and mortality.

Conflicts of Interest: The authors declare no conflicts of interest regarding the publication of this work.

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الملخص العربي

التأثير الوقائي للأجوميلاتين على بعض مؤشرات جهاز القلب الوعائى والتمثيل الغذائي في مرض السكري من النوع الثاني المستحث معمليا في الفئران

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ملخص البحث

الخلفية: لقد وجد أن معدل حدوث الاكتئاب أعلى بكثير لدى مرضى السكري مقارنة بعامة الناس. كما يعتبر عامل خطر مهم لبعض المضاعفات مثل مضاعفات القلب والأوعية الدموية لهؤلاء المرضى. وقد أظهر الاكتئاب ومرض السكرى ومضاعفاته على الأوعية الدموية الكبيرة علاقة ذات اتجاهين. أجوميلاتين (مضاد اكتئاب غير تقليدى) هو منشط لمستقبلات الميلاتونين ومضاد لمستقبلات السيروتونين، وقد ثبت أن له تأثير مضاد للالتهابات ومضاد للأكسدة

الهدف: تهدف الدراسة الحالية إلى إظهار التأثيرات الوقائية للأجوميلاتين على اضطرابات القلب والأوعية الدموية وارتفاع السكر في الدم.

الطرق: تضمنت الدراسة ثمانية عشر من ذكور الجرذان البيضاء وتم تقسيمهم إلى ثلاث مجموعات على النحو التالي: المجموعة الأولى: كانت بمثابة مجموعة ضابطة، المجموعة الثانية: مجموعة مرض السكري (غير المعالجين) حيث تم تحفيز مرض السكري عن طريق اعطاء الجرذان فركتوزتركيز 20٪ فى الماء لمدة 14 يومًا متبوعًا بحقنهم بالألوكسان بجرعة 150 ملغم/كغم، المجموعة الثالثة: مجموعة مرض السكرى المعالجة بالأجوميلاتين، يعطى الأجوميلاتين (20 ملغم / كغم / يوم) لمدة أربعة أسابيع متتالية. في نهاية الفترة التجريبية، تم الحصول على عينات الدم لتحديد الهيموجلوبين السكري، الجلوكوز، والأنسولين في الدم. وتم إجراء قياسات ضغط الدم وتخطيط القلب الكهربائي .بالإضافة إلى ذلك، تم إجراء التحليل النسيجي لأنسجة القلب والأورطى.

النتائج: أدى الأجوميلاتين إلى انخفاض كبير في ضغط الدم الشرياني مع تحسن في تغييرات تخطيط القلب . أدى نفس العلاج إلى انخفاض ملحوظ في نسبة الجلوكوز في الدم والهيموجلوبين السكري ومقاومة الأنسولين وارتفاع كبير في مستوى الأنسولين في الدم. بالإضافة إلى ذلك، تم تحسين التغيرات النسيجية في أنسجة عضلة القلب والأورطى.

الإستنتاجات: الأجوميلاتين له تأثير وقائي للقلب ضد تشوهات القلب في الجرذان المصابة بداء السكري والتي يمكن أن تتوسطها تحسين إرقاء الجلوكوز، واستعادة ديناميكا الدم، وتخفيف الالتهاب.

الكلمات المفتاحية: أجوميلاتين، أمراض القلب والأوعية الدموية، داء السكري.

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