Early Online

The European Research Journal 2025 Original Article

DOI: https://doi.org/10.18621/eurj.1644498 *Medical Physiology*

How does agomelatine affect contraction in rat myocardial tissue?

Raviye Özen Koca[1], Zülfikare Işık Solak Görmüş[1], Hatice Solak[2], Gülnur Akdoğan[1]

[1]Department of Physiology, Necmettin Erbakan University, Faculty of Medicine, Konya, Türkiye; [2]Department of Physiology, Kütahya Health Sciences University, Faculty of Medicine, Kütahya, Türkiye

ABSTRACT

Objectives: Cardiovascular diseases and depression are frequently seen together. Despite the developments in the treatment efficacy of agomelatine, a widely used antidepressant, its safety profile on cardiac tissue has not been sufficiently investigated. The aim of this study was to evaluate effects of agomelatine on contraction in rat myocardial tissue in depression and anxiety conditions frequently encountered in cardiovascular diseases and after cardiac surgery.

Methods: Myocardial tissue sections were removed from 12 male Wistar Albino rats divided into control and agomelatine groups. The tissues were placed in the isolated organ bath system. Maximum contraction was achieved by applying 10^{-1} M adrenaline to both groups. When the contraction plateaued, the same volume of vehicle as agomelatine were applied to the Control group. Agomelatine cumulative doses (10^{-8} – 10^{-4} M) were applied to the agomelatine group. The resulting isometric contraction forces were recorded by the isolated organ bath system. The statistical analyses of the study were performed with the R 4.3.1 program.

Results: A significant increase in the tension of the tissues was observed with adrenaline in both the Control and Agomelatine groups. In the Agomelatine group, the tension at 10^{-8} agomelatine dose was significantly lower compared to 10^{-1} M adrenaline dose ($P<0.05$), and tension at 10^{-6} agomelatine dose was significantly lower compared to 10^{-7} agomelatine dose ($P<0.05$).

Conclusions: Agomelatine produced a dose-dependent suppressed contractile response in myocardial tissue. This suggests that it may have positive effects on increased blood pressure, positive inotropic effect and hypertensive state, which can occur in cardiovascular diseases and are also common in depression. Agomelatine may have a more favorable side effect profile than other antidepressants in cardiovascular disease states.

Keywords: Agomelatine, antidepressant, cardiovascular disease, contraction, myocardium

Mood disorders often emerge in young adulthood. Anxiety and depression have been found to be associated with cardiovascular diseases (CVD) in young adults [1]. Unrecognized anxiety presents a significant challenge in cardiology. It may be essential to examine anxiety and its various subtypes in relation to the onset and progression of CVD. Anxiety disorders seem to elevate the risk of developing CVD and serve as an indicator of poor prognosis in individuals with existing CVD, regardless of

Received: March 18, 2025 **Accepted:** May 7, 2025 **Available Online:** June 4, 2025 **Published:** XX XX, 2025

How to cite this article: Özen Koca R, Solak Görmüğ ZI, Solak H, Akdoğan G. How does agomelatine affect contraction in rat myocardial tissue? Eur Res J. 2025. doi: 10.18621/eurj.1644498

Corresponding author: Raviye Özen Koca, MD., PhD., Assist. Prof., Phone: +90 332 221 05 00, E-mail: raviyeozen@gmail.com

the presence of depression. Understanding anxiety is crucial for uncovering the mechanisms behind cardiopathogenesis, formulating new treatment approaches, and implementing clinical interventions for those at risk of or already diagnosed with CVD [2]. Depression and anxiety frequently occur together in individuals with CVD. People with CVD are at a greater risk of experiencing depression compared to the general population. Likewise, individuals suffering from depression have an elevated likelihood of developing CVD over time and face higher mortality rates. Among CVD patients, those who also struggle with depression tend to have worse clinical outcomes than those without it. More severe depression is associated with an increased risk of death and other cardiovascular complications. Given how common depression is among CVD patients, there is likely a two-way connection, where CVD contributes to depression, and depression, in turn, worsens CVD and its prognosis. Since both depression and anxiety play a significant role in overall well-being, addressing them is essential in CVD management [3].

The effects of depression on the cardiovascular system can be listed as positive chronotropic effect, increased blood pressure, cardiac arrhythmia, platelet aggregation and negative effects on inflammation. It has been determined that antidepressants used in the treatment of depression cause a decrease in risk of coronary heart disease [4].

It has been reported that pineal gland dysfunction is involved in the pathogenesis of psychiatric disorders and that depression is associated with low melatonin levels. The fact that many antidepressant drugs increase norepinephrine and serotonin levels and thus increase melatonin levels is seen as evidence of the depression-melatonin relationship. It has also been thought that melatonin, released during night, may play an important role in balancing high blood pressure because it reduces blood pressure, heart rate [5]. In addition, physiological deficiency of melatonin can increase hypoxia and oxidative damage. The importance of melatonin use in heart diseases caused by oxidative damage can be emphasized. In an in vivo study conducted by Lee *et al*. [6], it was determined that intravenous melatonin administration prevented ventricular tachycardia, fibrillation and premature ventricular contraction.

Recent findings have shown that effects of melatonin on cardiovascular system. Melatonin causes vasodilation in peripheral vascular beds. Melatonin levels have been found to be low at risk of sudden death [7].

Agomelatine (Ago), a new melatonergic antidepressant drug, has good therapeutic effects on mood disorders and insomnia. Recent studies have shown the neuroprotective function of Ago, including its antiapoptotic and antioxidative effects. Ago is a 5-hydroxytryptamine receptor 2C (5HT2C) receptor antagonist and melatonin receptor (MT1-MT2) agonist. Melatonin also has protective properties in providing physiological conditions for the cardiovascular system [8]. Depression is a common comorbid disease in cardiac patients. Despite the developments in the treatment efficacy of Ago, a widely used antidepressant, its safety profile on cardiac tissue has not been sufficiently investigated. Detailed animal studies may be guiding in determining the cardiovascular side effects associated with the use of the drug. The aim of this study was to evaluate whether Ago, an antidepressant widely used in cardiovascular diseases and in depression and anxiety frequently encountered after cardiac surgery, affects the physiological properties (inotropy and chronotropy) of rat myocardium in a dose-dependent manner.

METHODS

Twelve male Wistar Albino rats aged 12 weeks (250-300 gr) were included in the study. The rats were kept in an environment with 12 hours of light and darkness, 24ºC room temperature and 55-60% humidity. The animals were given standard rat food and fresh water ad libitum throughout the experiment. After a seven-day acclimation period, study groups were formed.

For isolated organ bath studies, experimental animals were decapitated under anesthesia and myocardial tissue sections were separated and immediately placed in Krebs-Henseleit solution. The content of the Krebs-Henseleit solution to be used in the experiments is as follows: NaCl, KCl, $MgSO_4$, $KH2PO_4$, $CaCl_2$, $NaHCO_3$, glucose.

The isolated organ bath is defined as a system that includes the basic conditions that can sustain the vitality of isolated tissues under in vitro conditions. The isolated organ bath system includes: amplifier, chambers, isometric power converter, thermostatic circula-

Fig. 1. Protocol for isometric contraction recording. After 10^{-1} M adrenaline-induced maximal contraction, vehicle was added to Control (n=6) and cumulative agomelatine doses (10^{-8}–10^{-4} M) to the treatment group (n=6) at 10-minute intervals.

tion pump, O_2-CO_2 mixture tube, recording unit, liquid and gas transport apparatus. In the isolated organ bath system, Krebs solution is used to maintain the vitality of tissues. Krebs-Henseleit solution is a solution that provides the physiological conditions in vivo to a certain extent in vitro. Its content allows smooth muscle cells to maintain their contractile properties at an optimal level in vitro.

In the current project; 10 ml organ bath chambers heated at 37ºC and containing normal Krebs-Henseleit solution were continuously gassed with a mixture of 95% O_2 and 5% CO_2. Myocardial tissue sections obtained from the experimental animal were placed in the glass chambers in the isolated organ bath by applying 1 gr tension and then isometric contractions were recorded. This tension level was kept constant for all samples. Contractions of the tissues in the setup were recorded by following the amplitude and frequency of contractions with the isometric power converter and amplifier connection (BIOPAC MP36). The Krebs solution containing the tissues was renewed at 15-minute intervals.

The tissues taken from the experimental animals were divided into 2 groups as Group 1 (Control Group, n=6) and Group 2 (Agomelatine Group, n=6). After the tissues were hung, 10-1 M adrenaline was added to spontaneous isometric contractions and maximum contraction was achieved When the contraction reached a plateau, the same volume of vehicle as agomelatine was added to the chambers of the Control group at 10-minute intervals and 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4} M doses of Ago was added to the chambers of the Agomelatine group at 10-minute intervals. Muscle tension parameters were assessed 10 minutes before adrenaline was added, 10 minutes after adrenaline was added and after each dose of drug (Fig. 1) [9, 10].

Statistical Analysis

The statistical analyses of the study were performed with the R 4.3.1 program. Mean±standard error of mean (Mean±SEM) was calculated for numerical variables. $P<0.05$ was accepted as significant. Tukey-Kramer correction was used when statistical analyses were performed when necessary.

RESULTS

Contractions of rat myocardial tissue in isolated organ bath were recorded and statistically evaluated (Figs. 2 and 3). When the tension values recorded at Time3 ($P<0.05$), Time4 ($P<0.05$), Time5 ($P<0.05$), Time6 ($P<0.001$) and Time7 ($P<0.005$) were compared between the groups, significant differences were detected (Fig. 4).

The time-dependent change of the measured tensions showed significant difference between the groups ($P<0.001$). There were significant differences

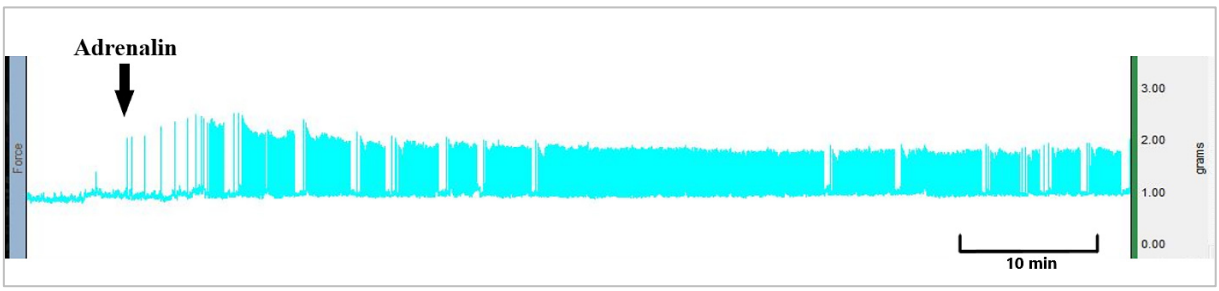

Fig. 2. Control group. At the time indicated by the arrows, adrenaline has been added to the chamber.

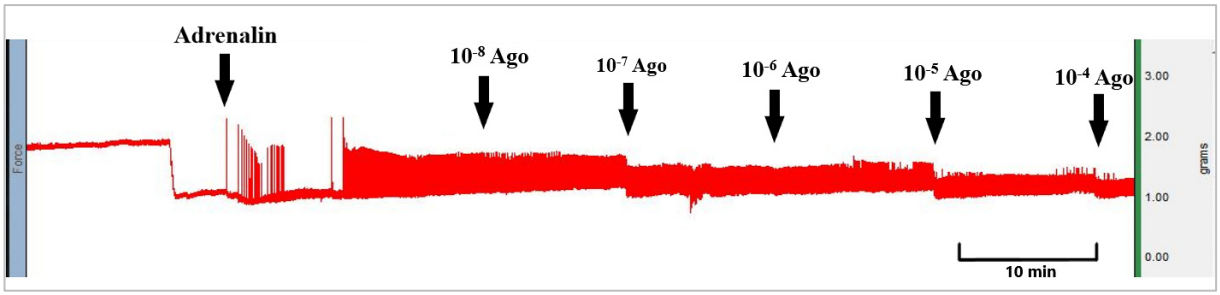

Fig. 3. Agomelatine group. Drugs were added to the chambers at the times indicated by the arrows.

between the tension values changing with time within the group (the tension values recorded at Time1 and Time2 ($P<0.001$), Time2 and Time3 ($P<0.05$), Time3 and Time4 ($P<0.05$), Time4 and Time5 ($P<0.05$), Time5 and Time6 ($P<0.05$) are significantly different from each other.

When the time-dependent changes in tension values were compared in pairs within the group, a significant difference was found between Time1 and Time2 in the control group ($P<0.005$). A significant difference was found between Time1 and Time2 ($P<0.005$), between Time2 and Time3 ($P<0.05$), and between Time4 and Time5 ($P<0.05$) in the agomelatine group (Fig. 4).

DISCUSSION

In the present study, the dose-dependent effects of agomelatine, an antidepressant commonly used in depression and anxiety conditions frequently encountered in cardiovascular diseases, on contraction in rat myocardial tissue were evaluated. Contraction forces of rat myocardial tissue were examined in an isolated organ bath system.

Ago was synthesized from melatonin as a melatonin analog among antidepressant agents [11]. Ago is a melatonergic agonist and 5HT2C antagonist [12]. Findings obtained in recent years have shown that effects of melatonin on cardiovascular system are recep-

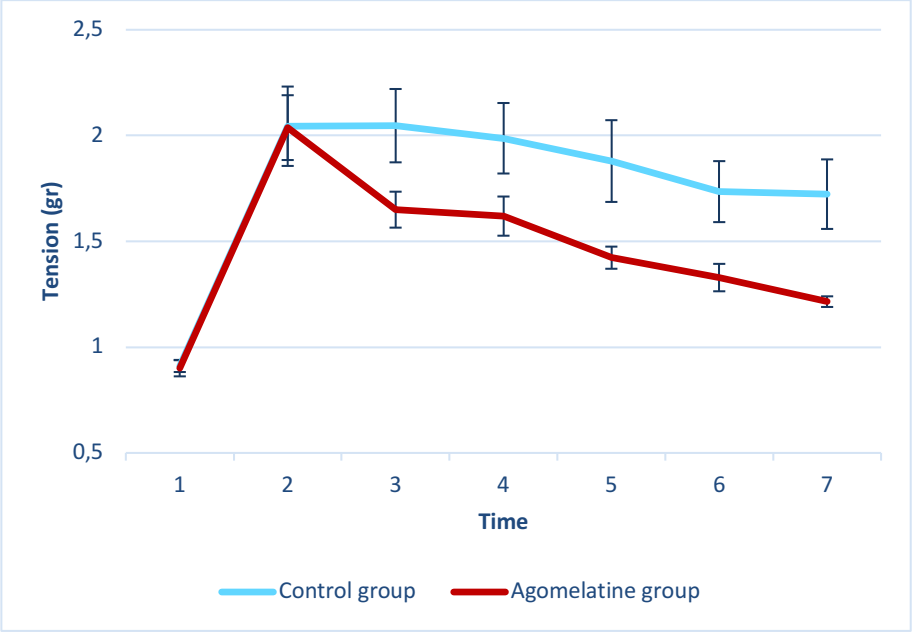

Fig. 4. Tension changes in rat myocardial tissues in response to adrenaline and agomelatine in isolated organ bath. Time 1: baseline; Time 2: 10^{-1} M adrenaline; Times 3–7: cumulative doses of agomelatine (10^{-8} to 10^{-4} M) were administered to the Agomelatine group, and vehicle to the Control group. Significant differences between groups were observed at Time 3, 4, and 5 ($P<0.05$), and at Time 6 and 7 ($P<0.005$). Time-dependent changes in tension values were significantly different between groups ($P<0.001$).

tor or non-receptor mediated. Melatonin causes vasoconstriction in cerebral arteries. Melatonin levels were found to be low in coronary heart disease patients at risk of myocardial infarction [13].

In a study, the possible healing effects of Ago on lipopolysaccharide-induced endothelial and cardiac damage were investigated. Lipopolysaccharide was shown to induce inflammation, oxidative stress, and apoptosis in cardiac and endothelial tissues. Ago improved all these parameters with its antioxidant, anti-inflammatory, and antiapoptotic activities [14]. In a different study, Ago significantly reduced hypertension-induced memory, endothelial function, nitrosative stress, mitochondrial dysfunction, inflammation, and brain damage disorders via MT1/MT2 and 5HT2C receptors [15].

Ago is a pharmaceutical compound that acts as an agonist for melatonin receptors with specific affinity for the MT1 and MT2 receptor subtypes. To evaluate the effect of this compound on contraction, various tissue contractions have been evaluated in different studies. The complex interaction between Ago and the modulation of estrous cycles, pregnancy periods, litter numbers and uterine contractions has been investigated in a study. Ago has been shown to inhibit spontaneous and oxytocin-induced myometrial contractions in a dose-dependent manner [16].

The results of the studies examining the effects of Ago on the contractions of the tissues belonging to the cardiovascular system are quite limited. Singh *et al*. [15] showed that 24-day Ago administration at a dose of 2 and 4 mg/kg can alleviate the suppressed relaxation of rat thoracic aortic tissue due to renovascular hypertension. In another study, Nurullahoğlu-Atalık *et al*. [17] stated that Ago caused a dose-dependent nitric oxide-mediated inhibition on intact rat thoracic aortic tissue contraction. In the current study examining its effect on cardiac contraction, Ago was shown to cause a significant inhibition in the increased tension of myocardial tissue induced by adrenaline, compared to the control, after each dose added. This reveals that the inhibitory effect of Ago on muscle contraction, which is also supported by other studies, is also effective in cardiac tissue. On the other hand, following the significant increase in the tension force of the tissues in both the Control ($P<0.005$) and Agomelatine ($P<0.005$) groups with adrenaline; the fact that the tension at Time3 was lower compared to Time2 ($P<0.05$) and the tension at Time5 was lower compared to Time4 ($P<0.05$) in the Agomelatine group suggests that the inhibitory effect of Ago may be dose-dependent. This result is important, as there is no other study proving this effect of Ago on cardiac tissue. When the current study and other limited research results are evaluated together, it is clear that Ago produces a dose-dependent suppressed contractile response in both cardiac and vascular tissue. This suggests that it may cause positive effects on increased blood pressure, positive inotropic effect and hypertensive status, which can occur in cardiovascular diseases and are also common in depression.

In the study conducted in the isolated rat heart model to examine the effects of Ago on myocardial ischemia reperfusion injury (MIRI), rat hearts were isolated and subjected to 30 minutes of ischemia and then 120 minutes of reperfusion to induce MIRI. Ago (10, 20 or 40 mg/kg) was injected intraperitoneally into the rats 1 hour before heart isolation. It was observed that Ago significantly improved cardiac function and alleviated pathological changes in the ischemic myocardium [18].

A different study was conducted to investigate the protective effects of Ago, a melatonin receptor agonist, against cadmium-induced toxicity. Ago significantly inhibited the cadmium-induced elevation of serum cardiac enzymes. Ago restored the structure of cardiac myofibrils and seminiferous tubules [19].

The cardioprotective effect of Ago on isoproterenol-induced myocardial damage and the role of nitric oxide in cardioprotection were investigated. Serum cardiac enzymes and cardiac tissue oxidative stress parameters were evaluated. It was observed that isoproterenol significantly increased serum cardiac enzymes and there was a significant increase in oxidative, inflammatory and nitrosative stress in myocardial tissue. Pretreatment with Ago significantly reversed these profound isoproterenol myocardial damaging effects. These results revealed that Ago protects against isoproterenol-induced myocardial damage through its antioxidant, anti-inflammatory and anti-apoptotic effects [20]. In experimental studies on parameters related to oxidative stress in rats, Ago was shown to have an antioxidant function similar to melatonin. In a study, electrocardiographic, biochemical and nuclear imaging data show that pretreatment with Ago attenuates doxorubicin-induced cardiotoxicity similar to

melatonin [21].

The data obtained for Ago indicate that it may have cardioprotective effects. The data from the studies conducted reinforce the conclusion that this protective effect of Ago is due particularly to its antioxidant effect. In the present study, the dose-dependent inhibition caused by Ago in the increased tissue contraction of the myocardium due to adrenaline is similar to the results of the decrease in vascular tissue tension shown by a limited number of similar studies. The partial dose-dependent reduction of the increase in the contractile response induced by adrenaline through Ago addition suggests that the use of this drug may have a positive effect in cardiovascular diseases associated with conditions such as depression and anxiety, where cardiac inotropic/chronotropic response is considerably increased. On the other hand, while studies have shown that nitric oxide is a possible mediator in the vascular tissue for the inhibitory effect of Ago on contraction [17], it is not clear which mechanism may play a role in cardiac tissue. In addition, while it is thought that the improvement caused by Ago in damaged cardiac tissue functions is due to its antioxidant, anti-inflammatory, and antiapoptotic effects [14], the mechanism of the inhibitory effect it caused on adrenaline-induced increased tissue contraction in healthy hearts in the current study is also unknown. In this context, more detailed studies are needed to elucidate the pathways through which Ago affects cardiac tissue contraction.

Limitations

The study was conducted on isolated heart tissue. These results may not fully reflect the effects observed directly in living organisms. The effect of agomelatine was evaluated only under laboratory conditions, which may vary depending on different physiological factors in the body. The results obtained with different dose intervals of agomelatine or longer treatment periods may be different. The molecular mechanism by which ago may inhibit myocardial mechanical activity has not been investigated.

CONCLUSION

The healing and positive effects of agomelatine, which have been demonstrated in limited studies, have been shown on cardiac tissue in cases of CVD. In the present study, it has been shown that Ago has an inhibitory effect on contraction in the increased increased tissue contraction of the myocardial tissue contraction induced by adrenaline. This suggests that the use of this drug does not pose a risk for mood disorders such as depression and anxiety and various cardiovascular diseases characterized by an increase in cardiac inotropic/chronotropic response, and may even lead to positive effects. Data from long-term studies in larger populations will be valuable for the use of Ago.

Ethical Statement

This study was approved by the Necmettin Erbakan University KONUDAM Experimental Medicine Application and Research Center Animal Experiments Local Ethics Committee (Decision no. 2025-002, date: 16.01.2025).

Authors' Contribution

Study Conception: RÖK, ZISG, HS; Study Design: RÖK, ZISG; Supervision: ZISG; Funding: RÖK, HS, ZISG; Materials: RÖK, GA; Data Collection and/or Processing: RÖK, GA; Statistical Analysis and/or Data Interpretation: RÖK, GA; Literature Review: RÖK; Manuscript Preparation: RÖK, GA and Critical Review: RÖK, ZISG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during the conduction or writing of this study.

Editor's note

All statements made in this article are solely those of the authors and do not represent the views of their affiliates or the publisher, editors, or reviewers. Any claims made by any product or manufacturer that may be evaluated in this article are not guaranteed or endorsed by the publisher.

REFERENCES

1. Patterson SL, Marcus M, Goetz M, Vaccarino V, Gooding HC.

Depression and anxiety are associated with cardiovascular health in young adults. J Am Heart Assoc. 2022;11(24):e027610. doi: 10.1161/JAHA.122.027610.
2. Tully PJ, Harrison NJ, Cheung P, Cosh S. Anxiety and cardiovascular disease risk: a review. Curr Cardiol Rep. 2016;18(12):120. doi: 10.1007/s11886-016-0800-3.
3. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. Eur Heart J. 2014:35(21):1365-1372. doi: 10.1093/eurheartj/eht462.
4. Gan Y, Gong Y, Tong X, et al. Depression and the risk of coronary heart disease: a meta-analysis of prospective cohort studies. BMC Psychiatry. 2014;14:371. doi: 10.1186/s12888-014-0371-z.
5. Macchi MM, Bruce JN. Human pineal physiology and functional significance of melatonin. Front Neuroendocrinol. 2004;25(3-4):177-195. doi: 10.1016/j.yfrne.2004.08.001.
6. Reiter RJ, Tan DX. Melatonin: a novel protective agent against oxidative injury of the ischemic/reperfused heart. Cardiovasc Res. 2003;58(1):10-19. doi: 10.1016/s0008-6363(02)00827-1.
7. Dubocovich ML, Markowska M. Functional MT1 and MT2 melatonin receptors in mammals. Endocrine. 2005;27(2):101-110. doi: 10.1385/ENDO:27:2:101.
8. Yao K, Zhao YF, Zu HB. Melatonin receptor stimulation by agomelatine prevents Aβ-induced tau phosphorylation and oxidative damage in PC12 cells. Drug Des Devel Ther. 2019 21;13:387-396. doi: 10.2147/DDDT.S182684.
9. Solak Gormus ZI, Eker CB, Solak H, Ozen Koca R, Ozdengul F. Does sertraline affect contraction in endothelium damaged aorta? Selcuk Med J. 2024;40(1):8-15. doi: 10.30733/std.2023.01688.
10. Isık B, Ozen Koca R, Solak Gormus ZI, Solak H, Özdemir A, Emeksiz A. Vasoactive effects of fluoxetine in rat thoracic aorta smooth muscle. Cukurova Med J. 2022;47(2):729-737. doi: 10.17826/cumj.1085783.
11. de Bodinat C, Guardiola-Lemaitre B, Mocaër E, Renard P, Muñoz C, Millan MJ. Agomelatine, the first melatonergic antidepressant: discovery, characterization and development. Nat Rev Drug Discov. 2010;9(8):628-642. doi: 10.1038/nrd3140. Epub 2010 Jun 25.
12. Sansone RA, Sansone LA. Agomelatine: a novel antidepressant. Innov Clin Neurosci. 2011;8(11):10-14.
13. Dubocovich ML, Markowska M. Functional MT1 and MT2 melatonin receptors in mammals. Endocrine. 2005;27(2):101-110. doi: 10.1385/ENDO:27:2:101.
14. Asci H, Ozmen O, Erzurumlu Y, Sofu A, Icten P, Kaynak M. Agomelatine protects heart and aorta against lipopolysaccharide-induced cardiovascular toxicity via inhibition of NF-kβ phosphorylation. Drug Chem Toxicol. 2022;45(1):133-142. doi: 10.1080/01480545.2019.1663209.
15. Singh P, Gupta S, Sharma B. Melatonin receptor and KATP channel modulation in experimental vascular dementia. Physiol Behav. 2015;142:66-78. doi: 10.1016/j.physbeh.2015.02.009.
16. Kacar E, Tan F, Sahinturk S, et al. Modulation of melatonin receptors regulates reproductive physiology: the ımpact of agomelatine on the estrus cycle, gestation, offspring, and uterine contractions in rats. Physiol Res. 2023;72(6):793-807. doi: 10.33549/physiolres.935064.
17. Nurullahoglu-Atalık KE, Kutlu S, Solak H, Ozen Koca R. Agomelatine-induced responses in rat aorta. IJBMSP. 2017;7(1):7-10.
18. Jia P, Liu C, Wu N, Jia D, Sun Y. Agomelatine protects against myocardial ischemia reperfusion injury by inhibiting mitochondrial permeability transition pore opening. Am J Transl Res. 2018;10(5):1310-1323.
19. Hafez HM, Waz S, El-Tahawy NFG, Mohamed MZ. Agomelatine ameliorates cadmium-induced toxicity through the modification of HMGB-1/TLR-4/NFκB pathway. Toxicol Appl Pharmacol. 2022;457:116313. doi: 10.1016/j.taap.2022.116313.
20. Khalaf HM, Abdalla AM, Ahmed AF, Abdel-Aziz AM. Role of nitric oxide in mediating the cardioprotective effect of agomelatine against isoproterenol-induced myocardial injury in rats. Naunyn Schmiedebergs Arch Pharmacol. 2020;393(10):1809-1823. doi: 10.1007/s00210-020-01860-y
21. Aygun H, Gul SS. Cardioprotective effect of melatonin and agomelatine on doxorubicin-induced cardiotoxicity in a rat model: an electrocardiographic, scintigraphic and biochemical study. Bratisl Lek Listy. 2019;120(4):249-255. doi: 10.4149/BLL_2019_045.