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Adverse effect of chronic oral intubation of MSG on ECG, Endothelin-1, Nitric oxide, ATP synthase activity, and some minerals in male rabbits

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ABSTRACT

Monosodium glutamate (MSG) is a food additive with many applications. This substance is toxic to the cardiovascular system. Therefore, the present study aimed to evaluate the impact of MSG on electrocardiogram alterations and some cardiac biomarkers. Twenty male rabbits were divided into two groups equally and randomly. Group one served as the control group and was intubated with tap water. The second group of rabbits received 8 mg/kg B.W of MSG orally for ten weeks. A cardiac puncture was performed to collect blood samples from rabbits in the 10th week of the experimental study to evaluate cardiac biomarkers. These included endothelin-1, troponin I, nitric oxide (NO), and enzyme activities such as ATPase and NO synthase in the serum. Furthermore, potassium, sodium, calcium levels, and electrocardiographic intervals (P, QRS, and T) were measured. The present study showed that cardiac troponin I, endothelin-1, ATP synthase, and NO synthase activity levels significantly increased in the MSG-treated animals, while NO synthase activity decreased significantly. Furthermore, the concentration of NO in the serum was found to decrease significantly. Additionally, there was a significant increase in hypernatremia and a significant decrease in hypokalemia. The electrocardiogram recordings of the MSG group showed prolonged waves (P, QRS, T) and intervals (ST, QT) compared to the electrocardiogram records of the control group. This study concluded that administering 8 mg/kg of intubated medication daily for 10 weeks impact the cardiac markers, leading to arrhythmia in the male rabbits.

Introduction

Natural sodium salts of L-form glutamic acid are known as food flavor enhancers. Saltiness, sweetness, bitterness, and sourness are all determined by L-glutamate, which also contributes to the umami taste (Wahdan and Shareef, 2016). Glutamate is present in a wide variety of foods. While there is no issue if monosodium glutamate (MSG) is present in small amounts in any one food, the problem escalates significantly if small amounts are consumed daily from various common foods. It is also challenging to identify which foods contain MSG because it is listed under various names (van den Berg *et al*., 2017; Niaz *et al*., 2018). Several studies have shown that MSG is toxic to the brain, liver, kidneys, thymus, and reproductive system (Ortiz *et al*., 2006; Pavlovic *et al*., 2009; Abass and Abd El-Haleem, 2011; Iamsaard *et al*., 2014). Moreover, MSG has been found to cause hyperphagia, obesity, asthma, memory impairment, and hypothalamic neuron damage after long-term intake (Von Diemen *et al*., 2006). There is strong evidence that dietary MSG contributes to obesity and the development of many diseases, as well as increased blood pressure and heart arrhythmias, including ventricular fibrillation, which can cause sudden death (Areas *et al*., 2019). The use of MSG has been found to contribute to obesity, diabetes, and cardiovascular disease, in addition to its known effects on metabolism (Shannon *et al*., 2017). Collison *et al*. (2011) argue that consuming glutamate can lead to obesity and heart disease.

Consumption of MSG-containing foods increases fatigue and the risk of atrial fibrillation (Areas *et al*., 2019). MSG may increase the risk of cardiovascular disease and cause toxicity to the heart when added to foods (Heil *et al*., 2020). Globally, cardiovascular disease (CVD) has the highest mortality rate. Many developing countries have the highest prevalence of cardiovascular disease. It is caused by a combination of multiple plaques in the arteries that affect the arterial blood vessels (Subramanian *et al*., 2003; Surekha *et al*., 2007; Marcus *et al*., 2009). However, there are virtually no reported studies and limited information on how MSG affects rabbit hearts. This study examined the effects of chronic oral intubation of MSG on the heart of male rabbits. By measuring serum biomarkers for cardiac and blood vessel damage (e.g., cardiac troponin-I, endothelin-1, nitric oxide, ATP synthase, and NO levels), along with some cations (K^+, Na^+, and Ca^{++}), the assessment of cardiac and blood vessel damage was conducted. P waves, QRS waves, and T waves were recorded, along with ST and QT intervals, using electrocardiographs

Materials and methods

Animals

This study was conducted on animals at Karbala University between November 2020 and April 2021 according to international guidelines for animal care and use, with approval number (Vet, No. 01, 11, 20). Sixteen male New Zealand rabbits, aged 6-7 months and weighing 1300-1500 g, were recruited for the study. They were randomly divided into two groups (8 rabbits per group): the control group and the treated group. The rabbits were housed in standard conditions with a regulated temperature of 25±3°C and maintained on a 12-hour light: dark cycle. They had free access to food and water. After a two-week adaptation period, the rabbits in the control group were fed without any supplementation. In contrast, the rabbits in the MSG group were orally administered 8 mg/kg body weight of MSG dissolved in water daily for 10 weeks (Rogers and Blundell, 1990). Blood samples were collected at 10 weeks using the cardiac puncture technique. Serum was prepared by slowly and gently drawing ten milliliters of blood into a gel tube using a disposable syringe. The tubes were left at room temperature for 30 minutes and then centrifuged at 3000 rpm for 15 minutes to separate the serum. Serum samples were transferred into Eppendorf tubes and frozen at -20°C till analysis.

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Biochemical analysis

Cardiovascular troponin I (cTnI) was measured using a kit manufactured by a Chinese company in Guangzhou (Adams *et al.*, 1994). A rabbit endothelin ELISA kit from Bioassay Technology Laboratory was utilized to quantify serum Endothelin-1 (ng/L), also referred to as Endothelin 1 (ET-1), following the procedure outlined by Goldie and Fernandes (2000). Estimation of serum nitric oxide concentration was measured using the method described by Csonka *et al.* (2015). ATP Synthase activity was quantified using the Rabbit ATP Synthase Subunit Alpha, Mitochondrial ELISA Kit from Bioassay Technology Laboratory following the method described by Meyrat and Von Ballmoos (2019). The serum levels of NO Synthase (ng/ml) (ENOs) were determined using the Rabbit Nitric Oxide Synthase 3, Endothelial ELISA Kit from Bioassay Technology Laboratory.

Estimation of serum minerals

Specific kits for measuring serum potassium (mmol/L) and sodium (mEq/L) concentrations were provided by the Egyptian Company for Biotechnology (S.A.E). Biolab SA France provided a kit for measuring serum calcium concentration (mEq/L).

Electrocardiogram recording

The recording was conducted using the electrical recording apparatus after shaving the hair ends of the animals and placing them on a wooden board specifically designed for this purpose, matching the size of the animals. A wooden panel was attached to the animal, pierced from all four sides. Special electrodes were then modified to fit the animal's limbs, and a gel material was applied to aid in delivering electrical impulses. The electrodes were installed calmly and accurately after calming the animal multiple times before taking readings. This was done to tame the animal, ensure it remained calm, and prevent it from entering a state of fear and panic. After establishing the connection, the animal was left undisturbed for 10 to 15 minutes to remain calm. The measurement was done based on the Einthoven Triangle method, using a 10 Mm/ Mv amplification force, 25 Mm/s electrical voltage, and a speed of ½ second. The ECG measurement was conducted without anesthesia, as shown in Fig.1. A special graph paper was used to depict the heart diagram, which was divided into large squares of five small squares each. Readings were taken vertically and horizontally. Readings were represented by vertical voltages on the axis. (1 Mm = 0.1 Mv) was the size of a small square. On the graph, time was represented on the horizontal axis. Clocks were used to represent time. Each square measured one millimeter, which was equivalent to 0.04 seconds. P waves represent depolarization in the atria, and their speed on the paper was consistent. Due to the thinner and smaller atrial muscles compared to the ventricular muscles, the amplifier was unable to amplify the electrical waves propagating and repolarizing in the atrium. Depolarization of the ventricular muscle was represented by the QRS complex wave. Repolarization of the ventricular muscle was indicated by the T wave, representing a relaxed state (Monitillo *et al.*, 2016).

Statistical Analysis

Data was analyzed using Prism 8 software. The normalized data were tested with the Shapiro–Wilk test. Treatment means were analyzed using a student t-test at a significance level of $P < 0.05$.

Results

Fig. 2 illustrates the mean value of serum protein cardiac biomarkers in the control and treated groups in the experimental study. The serum cardiac endothelin-1 value increased significantly (****P < 0.0001) after 10 weeks in the MSG-treated group (12.88 ng/ml) compared to the control group (10.03 ng/ml). Also, Fig. 3 shows a significant (****P < 0.0001) increase in the serum cardiac troponin-1 in the MSG group (0.085 ng/ml) compared to the control group (0.025).

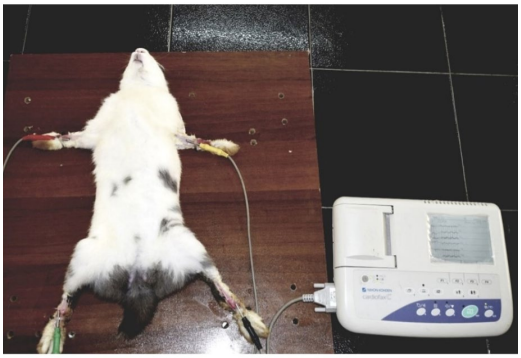

Fig. 1. Represents how to connect the electrodes in the electrical diagram of male rabbits. The red electrode corresponds to the right arm, the yellow electrode to the left hand, and the black electrode to the left leg, while the green electrode symbolizes the ground connector.

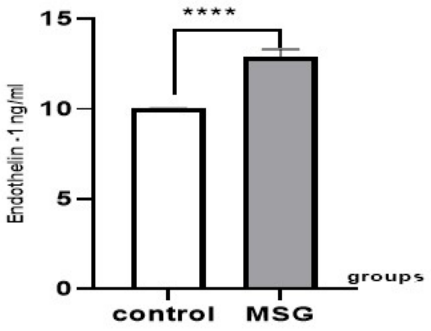

Fig. 2. Effect of daily oral intubation of MSG for 10 weeks on the serum endothelin-1 levels in male rabbits.

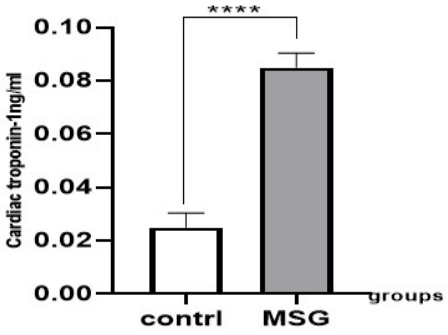

Fig. 3. Effect of daily oral intubation of MSG for 10 weeks on serum cardiac troponin-1 levels in male rabbits.

Fig. 4 illustrates a significant decrease in the serum NO levels (26.01 µ/ml) in the treated group compared with the control group. There was a significant difference in the activity of ATP synthase and NO synthase in the MSG group compared to the control (Fig. 5). There was a significant (****P < 0.0001) increase in ATPase activity to 169.41 ng/ml and a significant (***P < 0.0001) decrease in Nitric Oxide to 0.123 ng/ml in rabbits that received 8mg/kg daily for 10 weeks compared with the control group, which had levels of 0.236 ng/ml and 133.82 ng/ml, respectively.

Fig. 6 shows a significant increase (*** P<0.001) in the serum Ca levels (2.20 mEq/l) and Na levels (149.46 mEq/l) in the treated group compared to the control group levels of 2.08 mEq/l and 134.68 mEq/l, respectively. Additionally, the same figure demonstrated a significant decrease (****P<0.001) in the serum K concentration in the MSG group (2.09 mmol/l) compared to the control group (4.05 mmol/l).

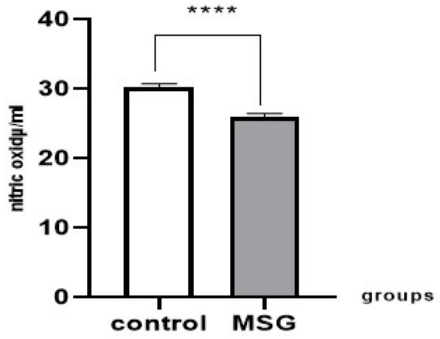

Fig. 4. Effect of daily oral intubation of MSG for 10 weeks on the serum nitric oxide levels in male rabbits.

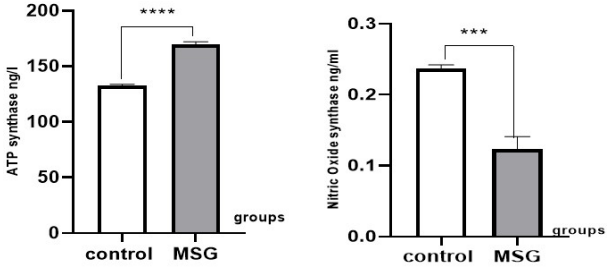

Fig. 5. Effect of daily oral intubation of MSG for 10 weeks on the serum ATPase and nitric oxide synthases in male rabbits.

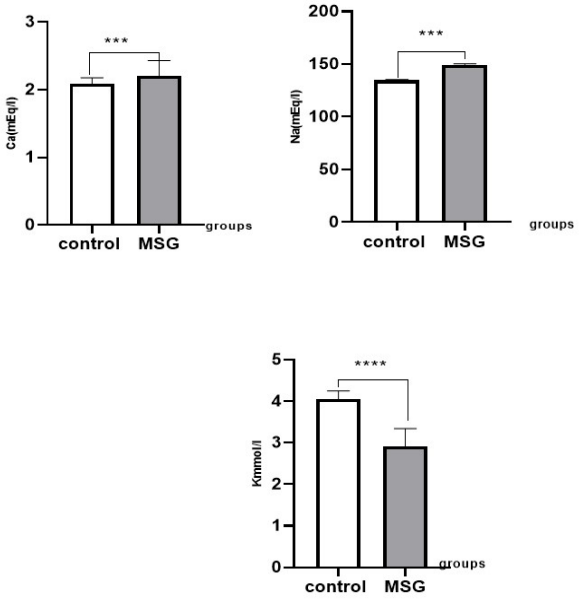

Fig. 6. Effect of daily oral intubation of MSG for 10 weeks on the serum levels of Ca, K, and Na in male rabbits.

There was a significant difference (**P < 0.001) in the QRS duration, with 4.91 seconds in the MSG group compared to 3.94 seconds in the control group. Also, there was a significant increase (****P < 0.001) in the mean value of the QRS waves in the MSG group at the end of the experiment, which was detected after 10 weeks in the MSG group (0.040 mV) compared to the control group (0.014 mV) (Fig. 7). The results of the current study revealed a significant increase (***P ≤ 0.001) in the P wave in the MSG group of 0.019 mV compared with the control group of 0.009 mV. Also, the same figure showed a significant increase in P-wave duration, from 1.09s in the control group to 1.33s (Fig. 8). Fig. 9 shows a significant increase (***P ≤ 0.001) in the T-wave amplitude in the MSG group (0.088 mV and 3.221 s) compared with the control group (0.07 mV and 2.571 s). Fig. 10 illustrates a significant increase in the ST intervals (0.128s) and QT intervals (0.140s) in the treated group compared to the control group (0.106s and 0.116s, respectively). Fig. 11 showed A significant decrease (****P ≤ 0.001) in the mean value of HR in the MSG group 207.442b/m compared to the control group 248.81b/m.

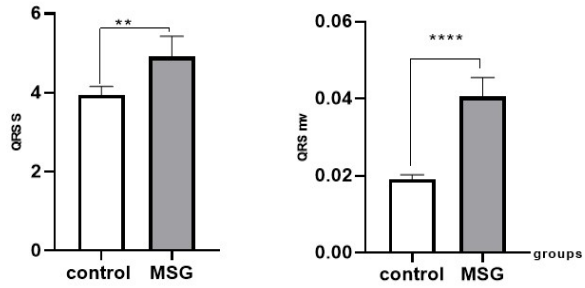

Fig. 7. Effect of daily oral intubation of MSG for 10 weeks on the serum QRST wave in male rabbits.

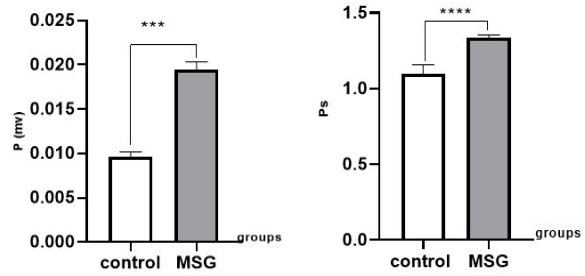

Fig. 8. Effect of daily oral intubation of MSG for 10 weeks on the serum P wave in male rabbits.

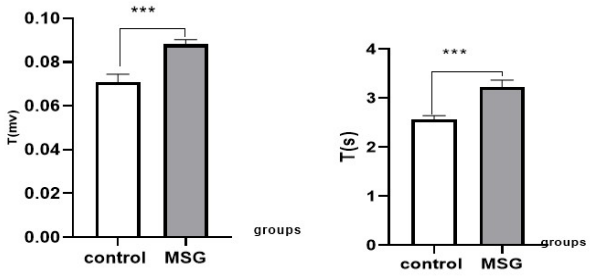

Fig. 9. Effect of daily oral intubation of MSG for 10 weeks on the serum T wave in male rabbits.

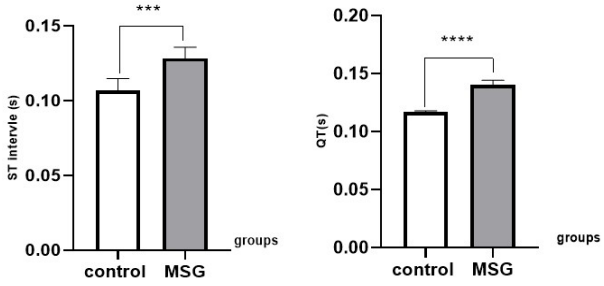

Fig. 10. Effect of daily oral intubation of MSG for 10 weeks on the ST and QT interval in male rabbits.

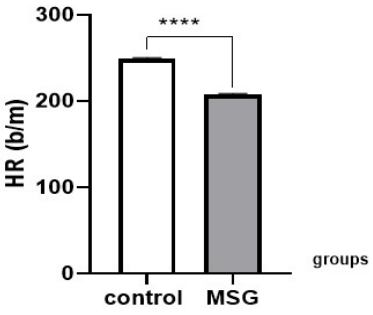

Fig. 11. Effect of daily oral intubation of MSG for 10 weeks on heart rate (HR) value (b/m).

Discussion

The current study showed a significant increase in Endothelin-1 in the group that received MSG, which agrees with Gorąca *et al.* (2011). There are three types of endothelins: ET-1, ET-2, and ET-3, each of which exhibits various biological activities. Polypeptide endothelin-1 is primarily synthesized by vascular endothelial cells and consists of 21 amino acids. A notable effect of this substance on smooth muscle is its potency as a vasoconstrictor and mitogenic agent (Heil *et al*., 2020; Haryono *et al*., 2022). Endothelin-1, secreted by endothelial cells, leads to a two- to threefold increase in plasma concentration of endothelin-1 (ET-1) in patients with heart failure, regardless of etiology (Haryono *et al*., 2022). The effects of ET-1 have been shown to increase oxidative stress by reducing glutathione and the antioxidant ratio GSH/GSSG, stimulating lipid peroxidation, and causing an increase in arterial permeability and myocardial water content (Heil *et al*., 2020). Oxidative stress contributes to atherosclerosis, heart failure, hypertension, and atherogenesis among cardiovascular diseases (Paravicini and Touyz, 2008).

The obtained results showed a significant increase in cardiac troponin I (cTnI) in the group that received MSG compared to the control group, which is consistent with the findings of Wahdan and Shareef (2016). Cardiac troponin is widely used to diagnose acute myocardial infarction as a marker for cardiac cell death (Heil *et al*., 2020). Myocardial ischemia can be predicted by elevated cTnI levels in patients experiencing stress, leading to tissue death and eventual infarction (Alpert *et al*., 2020). Rabbits treated with MSG and having elevated serum cTnI levels exhibited significant increases in serum CK-MB activity. A possible explanation for this could be attributed to the release of diagnostic markers of myocardial damage into the extracellular fluid when myocardial cells are damaged (Upaganlawar *et al*., 2009; Heil *et al*., 2020). Upon exposure to insufficient oxygen supply or nutrients, the cardiac membrane becomes permeable or may rupture, resulting in the leakage of cytosolic enzymes into the bloodstream. This leads to an increase in their serum concentration, inflammation, and the enhancement of adrenergic cardiac innervation. This process could determine the distribution of left ventricular coronary flows without coronary vessel obstruction (Kalogeris *et al*., 2016). However, serum cardiac troponin I (cTnI) levels in rabbits treated with MSG have not been reported in similar previous studies.

In oxidative stress conditions (Figs. 4 and 5), MSG promotes the release of reactive oxygen species (ROS) and decreases NO production by reducing NO-dependent relaxation and NO production. This indicates that the decreased relaxation induced by NO in MSG rabbits is not caused by a decrease in endothelial nitric oxide synthase (eNOS) expression but by a reduction in the enzyme's ability to produce NO (Villar *et al*., 2006). The data in this study revealed a significant increase in ATP synthase levels in the treated group compared to the control group, which is consistent with the study by Magi *et al.* (2013). The levels of ATP in cardiomyocytes have been shown to decrease significantly. The notice emphasizes the importance of maintaining mitochondrial ATP synthase to regulate energy balance within the heart. The ATP synthesis induced by glutamate increases when EAATs are expressed within mitochondria in various tissues (such as the brain and heart) and cell lines (Magi *et al*., 2012). If the ATP synthase cannot be up-regulated, there could be a mismatch between supply and demand in the heart, increasing the risk of heart failure (Long *et al*., 2015). Furthermore, the groups treated with MSG showed a significant reduction in NO synthase compared to the control groups. The results were consistent with those reported by Lobato *et al.* (2011). The level of relaxation induced by NO, as well as the concentration of NO products, decreased significantly in the samples treated with MSG. Endothelium-dependent vasodilation is reduced by the generation of ROS, which decreases the bioavailability of nitric oxide. ROS can be generated by uncoupled eNOS. An eNOS uncoupling occurs when the concentration of L-arginine, the substrate of NOS, or a cofactor of the enzyme depletes (Rochette *et al*., 2015). On the other hand, there was an increase in the expression of eNOS protein. This indicates a paradoxical increase in the expression of eNOS, instead of a decrease. This suggests that the reduced nitric oxide (NO)-dependent relaxation in the MSG group is not a result of decreased eNOS expression. Instead, it is associated with the decreased capacity of the enzyme to generate NO (Gbore *et al*., 2016).

Minerals such as potassium (K), sodium (Na), and calcium (Ca) were analyzed in the current study (Fig. 6). The data indicated a significant decrease in serum potassium concentration (hypokalemia) in the group that received MSG compared to the control group. This decrease in potassium levels in the extracellular fluid could be expected due to their impact on cardiac muscle. Even a slight decrease in potassium levels can lead to toxicity, causing a slow and irregular pulse. A myocardial infarction with hypokalemia has a clear relationship with ventricular fibrillation (Humphreys, 2007). As the potassium concentration (K^+) in the extracellular fluid decreases, the resting membrane potentials become hyperpolarized. Paradoxically, this leads to increased excitability of cardiomyocytes (Bers, 2001). Abnormal levels of potassium and calcium can lead to changes in the electrocardiogram (Joshi *et al*., 2004). Muscles in the heart are more susceptible to potassium than muscles in the skeletal system. Hypokalemia and hyperkalemia directly affect Na^+, Ca^{2+}, and K^+ balances (Takaoka, 2002). Heart hypertrophy and heart failure are both associated with increased intracellular sodium concentrations (Na^+), leading to elevated sodium levels in cells within the subsarcolemmal space (Despa, 2018; Aksentijević and Shattock, 2021). In addition, calcium can only act as a metabolic regulator and a second messenger if its concentrations are tightly regulated in both the cytosol and the mitochondria. The precise control of calcium permeability is an example of this regulation. Calcium permeability is usually very low, but it increases sequentially upon activation (Horn and Jaiswal, 2018). As a second method of extruding calcium from the cell, metabolic energy is consumed. This can occur through Ca^{2+}-dependent ATPases or $3Na^+$ lCa^{2+} exchange mechanisms, with energy derived from Na^+ gradients. The latter mechanism is a result of Na^+, and K^+-ATPases (Brini and Carafoli, 2011). In addition, calcium can also be bound or sequestered within the cell by energy-bind-dependent and energy-dependent mechanisms. Through the activation of mitochondrial Ca^{2+}-dependent dehydrogenases, an increase in (Ca^{2+}) could lead to a rise in cellular ATP content (Denton, 2009).

A study showed that oral administration of MSG to male rabbits for 10 weeks significantly increased the length of P, QRS, and T waves, as well as ST and QT intervals (Fig. 7, 8, 9, 10). Electrocardiograms (ECGs) are graphical representations of the heart's electrical activity over time. Despite their compact size, they provide a vast amount of valuable information. Electrical impulses are also generated by cardiac muscle activity, and muscle contraction, which creates the pulse, usually follows electrical activity. Therefore, a diet high in MSG can disrupt the conduction or depolarization of the atrium (Woodrow, 2010). Long QRS complexes indicate extended ventricular depolarization, while long QT intervals indicate longer intervals between depolarizations and repolarizations (Howarth *et al*., 2005). Consuming MSG can also contribute to changes in the QRS complexes, as well as the QT and QTc intervals. These electrocardiographic changes may be explained by polyuria, which is caused by osmotic diuresis resulting from increased glycemia (Howarth *et al*., 2005; Straus *et al*., 2006). A change in the voltage-dependent potassium ion channel may also be responsible for the increased QT interval. Elevated and low levels of serum potassium can promote cardiac arrhythmias due to their electrophysiological effects. The direct effects of potassium are not the only reason for this. The sodium-potassium ATPase and sodium-calcium exchanger also play an important role in regulating potassium, sodium, and calcium balances (Chan *et al*., 2015). Blocking Na+ channels lead to a widening of QRS complexes. The QRS complexes can exhibit bundle branch block signs in some cases (Joshi *et al*., 2004). Heart pacemaker cells, however, can be affected by Na^+ channel-blocking agents. The influx of sodium ions into pacemaker cells may slow down the depolarization of these cells, leading to bradycardia (Baky *et al*., 2009). An ECG can

be observed to show changes depending on calcium (Ca) and potassium (K) concentrations. There is evidence that fluctuations in potassium levels can alter the P wave and alter the conduction properties of the AV node, which may trigger arrhythmias (Pilia *et al*., 2017). The characteristic ECG changes associated with hypercalcemia and hypocalcemia are also caused by fluctuations in ionized serum calcium concentration. One of the main focuses of these changes is to describe the duration of ventricular depolarization and repolarization. The QT interval should be less than half the length of the R-R interval preceding it at the onset of the T wave. A prolonged QT interval is associated with delayed repolarization, which can lead to tachydysrhythmias and sudden cardiac death (Straus *et al*., 2006).

The heart rate (HR) of rabbits showed a significant decrease ($P < 0.01$) in the MSG group compared to the control group (Fig. 11). Administration of MSG led to a rapid decrease in heart rate, stabilizing at a new steady state after ten weeks. The decrease in heart rate may be partly explained by a decrease in physical activity. A reduction in the vagal influence on the heart may account for the diminished bradycardic reflex in rabbits treated with MSG. This reduction may suggest deficiencies in the vagal reserve utilized during heart rate responses triggered by baroreceptors. The reduction in this activity also results in reduced bradycardia (Howarth *et al*., 2005). As a result, the sinus node may have been less responsive to parasympathetic stimuli, thus attenuating the bradycardia response (Goldberger *et al*., 2019).

Conclusion

Based on the results of this study, the administration of MSG to male rabbits lowers serum levels of NO concentration and NO synthase activity, while increase serum troponin I, endothelin-1, and ATP synthase activity. The results of the electrocardiogram show prolonged waves (P, QRS, T) and intervals (ST, QT) in the MSG group. The current study found that prolonged daily oral intubation of 8 mg/kg of MSG for ten weeks led to the prolongation of arrhythmias. Male rabbits have shown a reduction in certain crucial cardiovascular biomarkers as a result of MSG exposure. A reduction in monosodium glutamate levels in processed foods is recommended, especially in products sold in supermarkets, restaurants, and homes.

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Conflict of interest

The authors have no conflict of interest to declare.

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