

Dietary Monosodium Glutamate Does Not Affect the Electrocardiographic Profiles of Diabetic and Nondiabetic Wistar Rats

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Abstract

Background and Aims: Some studies have recently indicated that dietary monosodium glutamate (MSG) is linked to obesity and the development of diabetes. Both diseases induce cardiovascular changes, such as increases in blood pressure and arrhythmias, including ventricular fibrillation, which may result in sudden death. Here, we aimed to investigate the effects of oral MSG administration on the electrical conduction and histological dysfunctions of the heart in control and diabetic Wistar rats. **Methods and Results:** Twenty-one-day-old Wistar rats were fed diets containing 0.0%, 1.0%, 2.5% or 5.0% MSG for 70 days. After this period, diabetes was induced with streptozotocin (STZ; 50 mg/kg bw) in half the rats and after an additional 21 days period; the electrocardiographic parameters and heart histology were evaluated. Diabetic rats demonstrated a reduction in heart rate as well as an enlargement of the QRS complex and QT and QTc intervals. Nevertheless, those changes are typical of STZ-induced diabetes, mainly because of electrolyte disturbances. The presence of MSG in the diet did not change the parameters evaluated between the group that received MSG and the group that did not receive MSG. Moreover, no histological alterations in the heart were observed due to MSG ingestion. **Conclusion:** Based on this evidence, diets containing MSG did not interfere with cardiovascular changes due to diabetes; there were no differences in the electrocardiographic and histological characteristics of the hearts of rats treated with MSG.

Keywords

Monosodium Glutamate, Diabetes, Cardiovascular Changes, Streptozotocin

1. Introduction

Monosodium glutamate (MSG), the sodium salt of glutamic acid, is widely used worldwide as an additive in foods (e.g. snacks, sauces and soups) to enhance their flavor by increasing taste perception [1] [2]. In addition, it has been highlighted out as a tool for reducing sodium in food products [3]. Glutamate is naturally present in the human body and has several important metabolic functions, which are mainly accomplished by regulating nitrogen metabolism and the energy supply and acting as a neurotransmitter in the central nervous system [4] [5] [6] [7]. Besides its known effects on metabolism, some studies have suggested that MSG is a compound that could foster the development of some diseases such as obesity and diabetes [8] [9].

In 1995, the FDA and the Federation of American Societies for Experimental Biology (FASEB) reviewed the scientific data related to the safety of MSG and concluded that there was no scientific evidence of adverse health effects in the general population caused by MSG. Despite this evaluation, a hypothesis has recently been raised linking obesity and heart disease to the consumption of elevated amounts of glutamate [10] [11]. The increasing prevalence of obesity contributes to the development of metabolic syndrome, a common metabolic disorder associated with type II diabetes and cardiovascular disease. In this regard, studies have attempted to elucidate the impact of MSG consumption on metabolism. High MSG and sucrose intake accelerate the development of type 2 diabetes in rats within 150 days of life [9]. The exposure of the enteroendocrine cell line to dietary concentrations of MSG for 72 hours reduces glucagon-like peptide-1 (GLP-1) secretion [8]. Finally, it was reported that MSG consumption in rats for 1, 3, 6 and 9 months reduces beta cell mass, although not enough to induce hyperglycemia [12]. Apart from the abovementioned studies, knowledge of the impact of MSG consumption on obesity and the development of diabetes is insufficient.

Diabetes is a multifactorial disease characterized by hyperglycemia that results from impaired insulin secretion, signaling and degradation [13] [14] [15]. In type 1 diabetes, the immune system attacks pancreatic beta cells, resulting in the absence of insulin and hyperglycemia [16]. While type 1 diabetes accounts for only 10% of the total population with diabetes, it accounts for 80% - 90% of diabetes in children and adolescents [17]. Diabetic alterations increase the risk of developing cardiovascular diseases and neuropathies, which represent one of the major causes of death of patients with diabetes [18] [19].

The prevalence of cardiac disease is elevated in diabetic patients, resulting in the main cause of death [20]. An electrocardiogram (ECG) is the most common cardiovascular diagnostic procedure [21], particularly because ECGs provide ample information while consuming relatively little space. An ECG is a time/voltage graph of the electrical activity of the heart. Cardiac muscle activity also generates electrical impulses, and muscle contraction, which creates the pulse, usually follows electrical activity. Although there are many factors that can influence car-

diac function, measurement of the time of electrical conduction and the voltage involved usually indicates the function, with different parts of the ECG complex representing different stages of conduction [22]. The normal sinus rhythm complex comprises a P wave, PR interval, Q wave, QRS complex, ST segment, T wave and occasionally a U wave. In this study, the P wave, PR interval, Q wave and QRS complex were evaluated because these parameters can be altered in patients with diabetes [22].

The intake of MSG through food, particularly after the consumption of Chinese food, has been associated to unpleasant symptoms such as headache, sweating, skin flushing, numbness or burning in the mouth, numbness or burning in the throat, nausea, fatigue and the onset of atrial fibrillation (AF) [23] [24]. Nevertheless, studies have failed to proof a connection between MSG and those symptoms, including the association of MSG with AF, a common cardiac arrhythmia, in self-reported MSG-sensitive patients [25]. However, since several subtypes of glutamate receptors (GluRs) are widely and differentially expressed in humans cardiac structures and each had a specific distribution, these receptors may be involved in important cardiac functions (such as contraction, rhythm, coronary circulation) and consequently may be implicated in the pathobiology of cardiac diseases [26]. Therefore, the GluRs in the heart could be targets for the effects of MSG being used as food additive and therefore should be considered for the safety evaluation of this flavor enhancer.

Thus, taking into consideration the possible association of type 1 diabetes and cardiovascular disease with the ingestion of MSG as food additive, the aim of this study was to investigate the effects of MSG oral administration on the electrical conduction and histological dysfunctions of the heart in diabetic and non-diabetic Wistar rats.

2. Materials and Methods

2.1. Animals

Healthy male Wistar rats, 21 days old, acquired at the animal distribution center of UNICAMP, were used in this study. The experimental protocol was approved by the Ethics Committee for Animal Experimentation of the Biology Institute, IB/UNICAMP (Protocol n° 1075-1). During the entire experimental period, the animals were housed in the Animal Facility of the University of Campinas (UNICAMP) under standard conditions of temperature ($21^{\circ}\text{C} \pm 2^{\circ}\text{C}$) and humidity ($55\% \pm 10\%$) with a 12-hour light/dark cycle and food and water provided *ad libitum*. Animal care were in accordance with basic principles of animal experimentation (Ordinance IB 05/2017 and 18/2016). Body weight and food consumption were measured at the beginning and the end of the experimental period. The control group (C) received a commercial diet (Labina-Purina-Paulínia, SP, Brazil), and the other groups received the commercial diet plus 1.0%, 2.5% and 5.0% MSG (1 g MSG + 99 g food, 2.5 g MSG + 97.5 g food and 5.0 g MSG + 95 g food, respectively) for a period of 70 days. At the end of this period, di-

abetes was induced in all rats. Then, the animals (weighing $326.0 \text{ g} \pm 16.0 \text{ g}$) were separated into eight groups ($n = 6$) and maintained on the same diets in metabolic cages for an additional 21 days. The eight groups were as follows: C (nondiabetic/commercial diet), C-MSG 1.0% (nondiabetic/1.0% MSG diet), C-MSG 2.5% (nondiabetic/2.5% MSG diet), C-MSG 5.0% (nondiabetic/5.0% MSG diet); D (diabetic/commercial diet), D-MSG 1.0% (diabetic/1.0% MSG diet); D-MSG 2.5% (diabetic/2.5% MSG diet) and D-MSG 5.0% (diabetic/5.0% MSG diet). Diabetes was induced by streptozotocin (STZ). For this purpose, a freshly prepared solution of STZ (50 mg/kg bw) in 0.1 M citrate buffer, pH 4.5, was injected intraperitoneally into rats that had faster overnight. After 24 hours, each streptozotocin-treated rat was evaluated for hyperglycemia by measuring its glucose concentration using the Accutrend GCT method (Roche Diagnostics®-Berna, Switzerland), and a blood sample was collected from the tail vein. All animals showed marked hyperglycemia (glucose > 200 mg/dl). Insulin (Novolin L 100 IU/mL; Novo Nordisk A/S; Bagsvaerd, Dinamarca) was injected intraperitoneally every two days. The experimental protocol used in this study is shown in **Figure 1**.

2.2. Electrocardiogram

Anesthetized rats (sodium pentobarbital, 40 mg/kg bw) were kept in the supine position with spontaneous breathing for the ECG recording. The electrodes were connected to computer channels (Heart Ware System, Heart Ware International

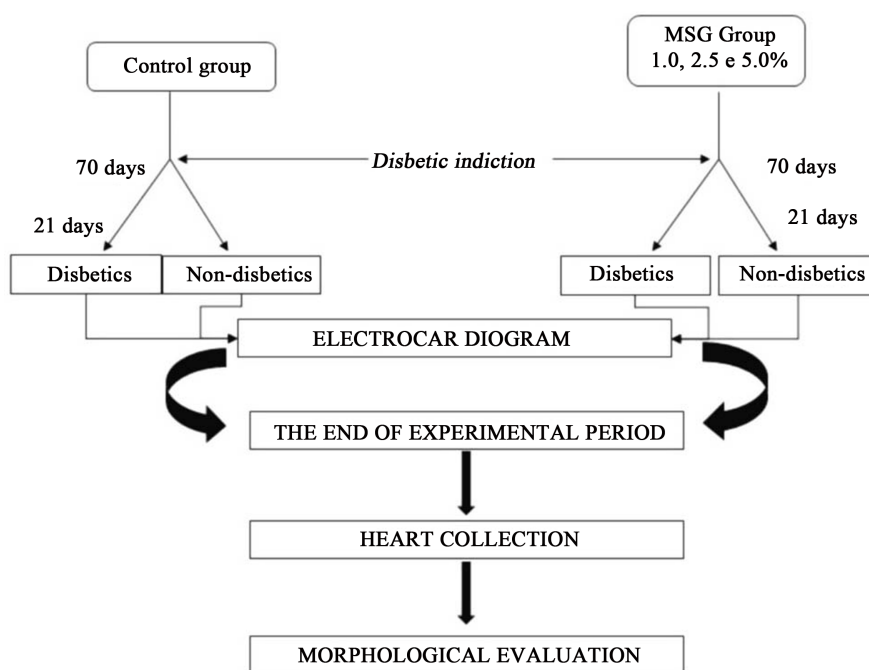


Figure 1. The experimental protocol. The control group received a commercial diet, and the MSG group received the commercial diet plus 1.0%, 2.5% and 5.0% MSG for a period of 70 days. Diabetes was induced with streptozotocin in half the animals at day 70, and after 21 days, the experiments were performed.

Inc, Framingham, Massachusetts, USA), and six standard waves (I, II, III, aVR, aVL and aVF) were recorded with 2N sensitivity at a speed of 50 mm/second. The P wave amplitude, PR interval and QT interval were measured for three consecutive beats from the beginning of the QRS complex to the point of the return of the T wave to the isoelectric line, defined as the TP segment. The QT interval was corrected for heart rate using Bazett's formula [27].

2.3. Morphological Evaluation

The hearts of the rats were collected for morphological evaluation at the end of the study. Fragments of the left ventricle were removed, stored in a 37% formaldehyde solution, and subjected to routine histological examination using the hematoxylin-eosin method [28].

2.4. Statistics

The GraphPad Prism program, version 6.0 (2012), was used for statistical analyses with a random block design according to the animals' weights. Two-way variance analysis (ANOVA) was used to determine statistical significance, and the Tukey test was used to compare the means of significant values, with a probability of 5%.

3. Results and Discussion

3.1. STZ Induction of Diabetes in Rats

The treatment of young adult rats with STZ produces a diabetic state that is characterized by weight loss, polydipsia, polyuria, glucosuria, polyphagia, hypoinsulinemia and hyperglycemia [29] [30]. The pathophysiology of STZ-induced diabetes includes a cardiomyopathy that is frequently associated with contractile dysfunction and heart rhythm disturbances [31]. In this study, diabetes was induced with STZ and confirmed by elevated blood glucose level (491.4 ± 48.8 mg/dL).

3.2. Effect of Dietary MSG on Body Weight

The presence of MSG in the diet, at concentrations up to 5.0%, had no effect on the body weight in the nondiabetic or diabetic rats (**Figure 2**), as previously described [30]. Contradictory results with respect to the relationship between body weight gain and the consumption of an MSG-containing diet have been reported in rats. Hermanussen (2006) [10] reported that the ingestion of MSG increased body weight gain and food consumption. On the other hand, in a study using Sprague-Dawley rats fed with diets of varying caloric density, fat content and carbohydrate content, Kondoh and Torii (2008) [32] reported a significant difference in body weight gain between rats that drank a 1.0% MSG solution and those that drank only water; they concluded that the voluntary ingestion of an MSG solution reduced weight gain and had no effect on food intake.

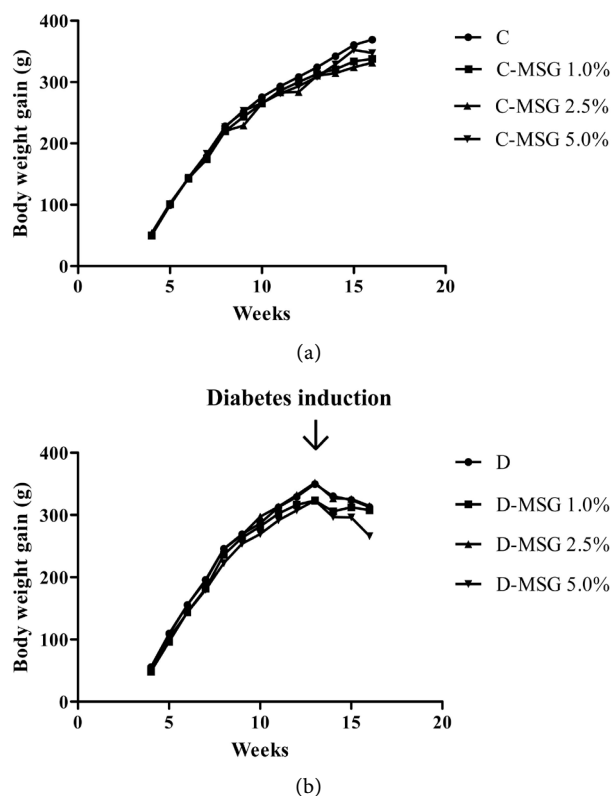


Figure 2. Body weight (g) in the nondiabetic (C group) and diabetic (D group) Wistar rats fed diets containing 0.0% - 5.0% added MSG. Data represent the mean \pm SEM ($n = 6$). * $P \leq 0.05$ vs CON. One-way ANOVA, $\alpha = 5\%$, GraphPad Prism 5.0.

3.3. MSG and Heart Rate

The sinoatrial node (SA) normally serves as the cardiac pacemaker, initiating electrical impulses and setting the heart rate. There were no significant differences in heart rate (HR) between the control and MSG-fed animals in the nondiabetic and diabetic groups. Nevertheless, the HR of diabetic rats was lower (272.6 ± 14.6 beats/min) than that of nondiabetic rats (329 ± 6.8 beats/min) (Figure 3). These results corroborate those of Howarth *et al.* (2005) [31], who reported that the HR declined rapidly after the administration of STZ, reaching a new steady state after 1 week, at which it remained for up to 20 days. A decrease in physical activity may partly underlie this reduction in HR.

3.4. Dietary MSG, Atrial Depolarization and the Conduction of Electrical Stimuli

The reduction in HR in the STZ-induced diabetic rats may be caused by a prolongation of the action potentials in the sinoatrial node, which in turn may be induced by the altered expression and/or function of the ion channels. In addition, STZ itself may directly contribute to heart rhythm disturbances [33]. Despite these observations, the addition of MSG to the diet at the concentrations studied did not change the action potential generation rates in the cardiac pacemakers in nondiabetic and diabetic rats.

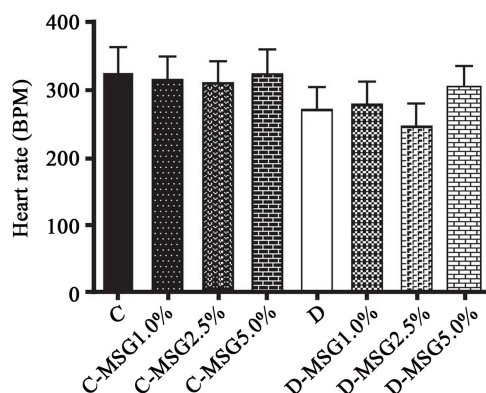


Figure 3. Heart rate (BPM) in the nondiabetic (C group) and diabetic (D group) Wistar rats fed diets containing 0.0% - 5.0% added MSG. Data represent the mean \pm SEM (n = 6). * $P \leq 0.05$ vs CON. One-way ANOVA, $\alpha = 5\%$, GraphPad Prism 5.0.

The amplitude of the P wave and the PR interval (**Figure 4**) were not significantly different between the control and MSG-fed rats in the nondiabetic and diabetic groups. Furthermore, there was no significant difference between non-diabetic and diabetic animals fed with the diets containing MSG. Impulses from the SA node spread out across the atrial muscle and are conducted from one muscle cell to the next. The P wave represents atrial depolarization, and the PR interval includes the P wave and the period of electrical standstill created by the impulse crossing the AV node [22]. Thus, diets containing up to 5.0% MSG did not alter atrial depolarization or the conduction of electrical stimuli from the atria to the ventricle.

3.5. Dietary MSG and QRS Complex, QT Interval and QTc

The main clinical manifestation of diabetic cardiomyopathy is a higher incidence of cardiac arrhythmias, including ventricular fibrillation, and a higher occurrence of sudden death because of alterations in ventricular repolarization. These alterations may cause changes in cardiovascular physiology and structure, which can be recorded by ECG. One of the most common problems detected in diabetic patients is the prolongation of the QRS complex, QT interval and QTc [34]. The QRS complex represents ventricular depolarization, and it is the largest component of the sinus rhythm complexes because a large voltage is required for ventricular depolarization. A specialized conduction pathway composed of the His bundle, bundle branches, hemi-branches and Purkinje fibers ensures that impulses travel quickly from the AV node to the ventricular muscle. The QT interval, representing the total ventricular depolarization and repolarization time, is measured from the beginning of the Q wave to the end of the T wave and should be less than half the time of the preceding R-R interval. Prolonged QT intervals represent delayed repolarization, which may cause tachydysrhythmias and sudden cardiac death [35].

The results obtained for the QRS complex, QT interval and QTc are illustrated in **Figure 5**. There were no differences in any of these parameters between the

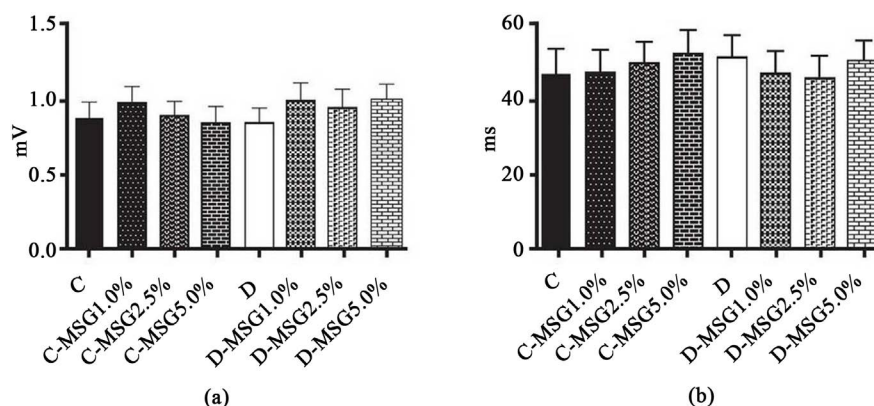


Figure 4. P wave amplitude (a) and PR interval (b) in the nondiabetic (C group) and diabetic (D group) Wistar rats fed diets containing 0.0% - 5.0% added MSG. Data represent the mean \pm SEM ($n = 6$). * $P \leq 0.05$ vs CON. One-way ANOVA, $\alpha = 5\%$, GraphPad Prism 5.0.

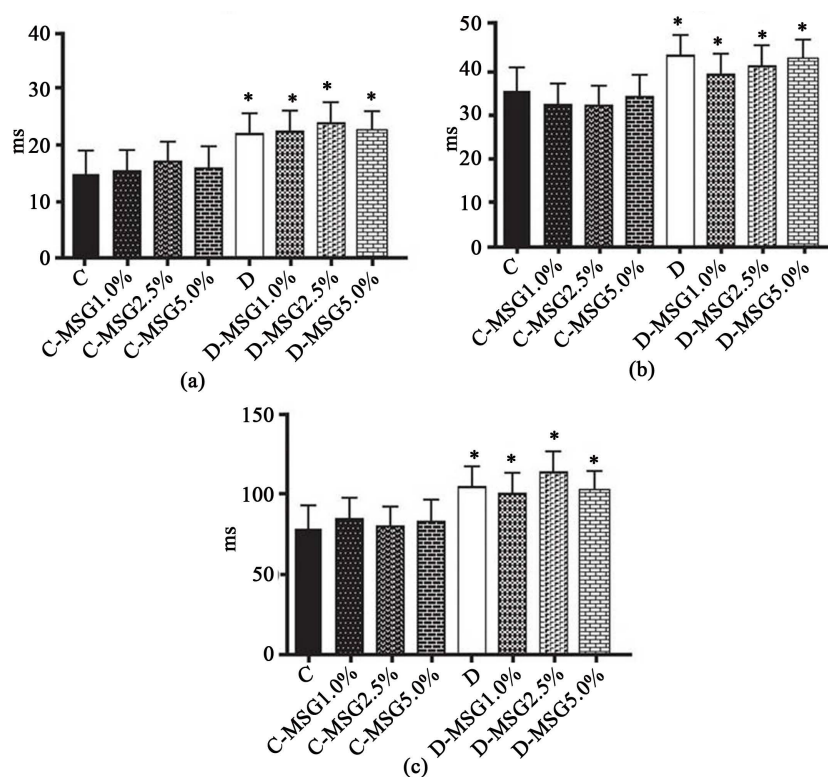


Figure 5. QRS complex (a), QT interval (b) and QTc interval (c) in the nondiabetic (C group) and diabetic (D group) Wistar rats fed diets containing 0.0% - 5.0% added MSG. Data represent the mean \pm SEM ($n = 6$). * $P \leq 0.05$ vs CON. One-way ANOVA, $\alpha = 5\%$, GraphPad Prism 5.0.

control and MSG-fed rats in both the nondiabetic and diabetic groups. However, the rats in the diabetic group showed significant increases in the QRS complex, QT interval and QTc when compared with the rats in the nondiabetic group ($P < 0.05$), although this result was irrespective of the addition of MSG to the diet. These findings are consistent with the results of previous studies with STZ-induced

diabetic rats [31]. A prolonged QRS complex indicates a prolongation of ventricular depolarization, and a prolonged QT interval indicates prolongation of the events between depolarization and repolarization [31]. In fact, the direct actions of STZ may also contribute to these heart rhythm disturbances.

The prevalence of QT prolongation has been reported to be as high as 16% and 26% in patients with type 1 and type II diabetes, respectively. Diabetic patients with more pronounced QT abnormalities tend to be older and have higher blood pressure levels and more cardiovascular complications [36].

3.6. Dietary MSG and Histological Pattern of the Heart

Although prolongation of the QRS complex and a prolonged QT interval could be the result of cardiac hypertrophy [27], the histological evaluations of the rat hearts did not reveal any significant differences between the nondiabetic and diabetic groups. All groups presented irregular nuclei located in the center of the cells and spaces between the fibers, both of which are typical characteristics of a normal heart (Figure 6 and Figure 7). In addition, the cardiac cells had similar sizes in all the studied groups. Therefore, there was no evidence of cardiac hypertrophy observed in the rats from either the nondiabetic group or the diabetic group.

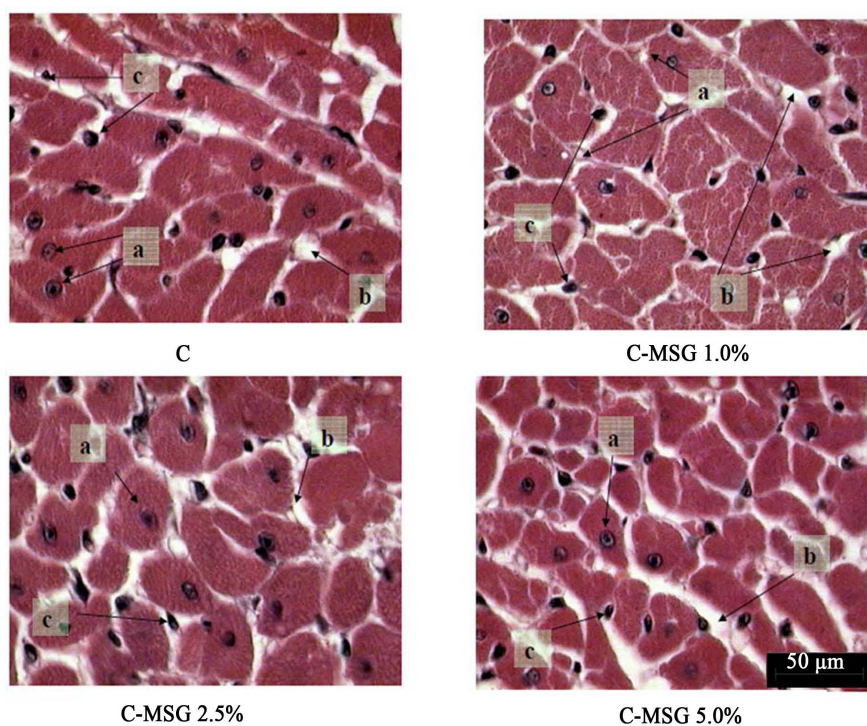


Figure 6. Photomicrograph of cross-sections of the left ventricle, by hematoxylin-eosin method, from nondiabetic (C group) Wistar rats fed diets containing 0.0% - 5.0% added MSG. The hearts from control rats were stained with HE. Irregular nuclei in the cell center (a) and spaces between the cardiac fibers (b), both typical of a normal heart, were found in both groups. Nuclei located outside the cardiac fibers belong to endothelial cells and fibroblasts (c). Intercalated disks mark the junctions between the cardiomyocytes.

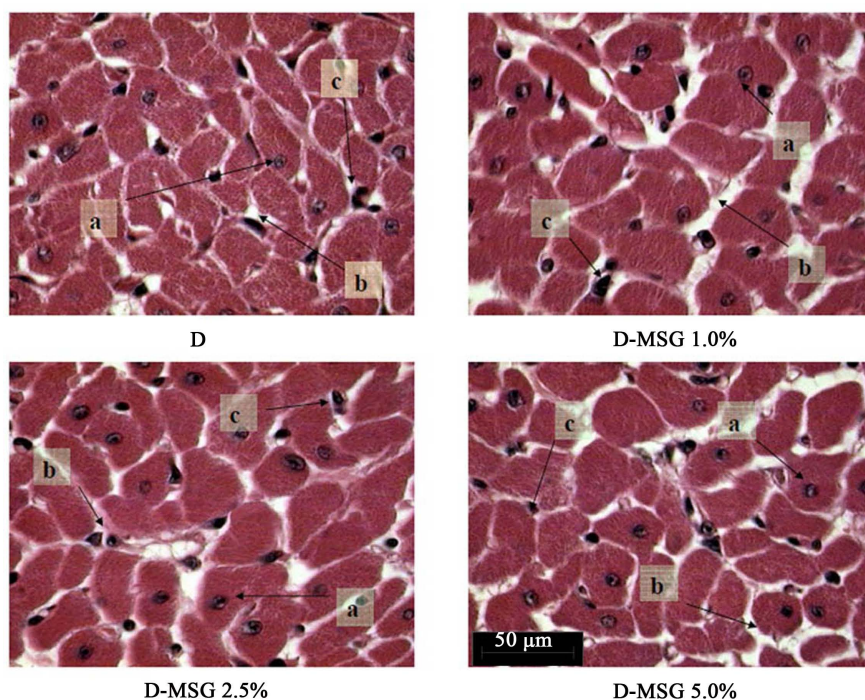


Figure 7. Photomicrograph of cross-sections of the left ventricle, by hematoxylin-eosin method, from diabetic (D group) Wistar rats fed diets containing 0.0% - 5.0% added MSG. The hearts from diabetic rats were stained with HE. Irregular nuclei in the cell center (a) and spaces between the cardiac fibers (b), both typical of a normal heart, were found in all groups. Nuclei located outside the cardiac fibers belong to endothelial cells and fibroblasts (c). Intercalated disks mark the junctions between the cardiomyocytes.

Given these data, we believe that the changes in the QRS complexes and, consequently, in the QT and QTc intervals in the diabetic animals fed the control diet or the diets containing up to 5.0% MSG are the consequences of hydroelectrolytic alterations that are typical of diabetes. In fact, such electrocardiographic alterations may be explained by the polyuria generally observed in diabetics, which is caused by osmotic diuresis as a result of the increase in glycemia [37]. This excessive urinary loss causes a decrease in potassium and other electrolytes, which could be responsible for the increase in the membrane repolarization period represented by a prolonged QT interval. The increased QT interval may also be the result of changes in voltage-dependent potassium ion channels [27] [31]. In fact, diabetes can alter the magnitude of the potassium channels involved in the repolarization process of the cardiomyocyte membrane [38], thereby affecting cardiac tissue.

4. Conclusion

Sub-chronic exposure (70 days) of Wistar rats to diets containing MSG (at concentrations of up to 5.0%) and subsequent STZ-induction to diabetes and maintenance of exposure (to the same diets containing MSG) for a further 21 days period, did not influence the electrocardiographic profile of the diabetic rats nor did it interfere in the stimulation and electrical conduction of the heart or

showed evidence of cardiac hypertrophy, in comparison to nondiabetic animals. Thus, this manuscript presents a consistent data about the effect of MSG on diabetic heart profile. However, some limitations such as analysis of heart lipid and glucose metabolism, as well as expression of proteins and ion channels involved in heart profile are not addressed. Additional studies are necessary in order to fully elucidate the effects of dietary MSG on diabetic subjects.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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