Research Article

Interaction Effect of Social Isolation and Taurine Doses on *in vivo* Cardiac Electrical Activity in Rat

Chinar Mustafa Mohammed[1]*, Thamer M. Bashir[1], Omar A.M. Al-Habib[2], Farhad Ramadhan[1], Mohammed Bassam[1]

[1]Department of Biology, Faculty of Science, University of Zakho, Zakho, Kurdistan Region, Iraq; [2]College of Science, Nawroz University, Duhok, Kurdistan Region, Iraq.

Abstract | Taurine, a ubiquitous endogenous sulfur-containing amino acid, possesses numerous pharmacological and physiological actions, including antioxidant activity, modulation of calcium homeostasis, and antiapoptotic effects. There is mounting evidence supporting the utility of taurine as a pharmacological agent against heart disease, including chronic heart failure. This study investigated the potential protective effects of taurine, on behavior and cardiovascular function in the male rat following arrhythmia induced by the social stressor. Here, we studied levels of heart electrical activity following experimental conditions: Cage control, social isolation in standard rat housing for 14 days, and pharmacokinetics effect of intravenous administration of different doses of taurine on arrhythmia induced by social isolation *in vivo* after. The ECG signals and parameters were recorded and analyzed with the aid of Bio Amp of ADInstruments data acquisition system and LabChart software. The results showed infusion of Taurine 1mg/kg/hr, 2.5mg/kg/hr and 10mg/kg/hr non significantly change heart rate (BPM), QRS intervals, S amplitude (mV), T amplitude (mV), ST height (mV), JT height (mV), QT intervals (s) and QTc (s).

Keywords | ECG, Taurine, Isolation, Heart rate, QRS

Received | January 08, 2022; **Accepted** | May 08, 2022; **Published** | June 16, 2022
***Correspondence** | Chinar Mustafa Mohammed, Department of Biology, Faculty of Science, University of Zakho, Zakho, Kurdistan Region, Iraq; Email: chinar.mohammad@uoz.edu.krd
Citation | Mohammed CM, Bashir TM, Al-Habib OAM, Ramadhan F, Bassam M (2022). Interaction effect of social isolation and taurine doses on in vivo cardiac electrical activity in rat. Adv. Anim. Vet. Sci. 10(6):1406-1413.
DOI | https://dx.doi.org/10.17582/journal.aavs/2022/10.6.1406.1413
ISSN (Online) | 2307-8316

INTRODUCTION

Cardiovascular diseases consider a common illness worldwide the main reason for death and, is a community health problem (Ibrahim et al., 2020; Yousry et al., 2021). One of the important investigational tools used in experimental cardiology is rat electrocardiography. The criteria for differentiating significant from insignificant variations in ECG parameters in rats, but on the other hand, still have to be established. Heart arrhythmias, often known as tachycardias or bradycardias, are abnormalities in cardiac rhythm caused by impulse disorders or a mix of the two (Durham and Worthley, 2002a).

Laboratory animals' social isolation serves as a model for the absence of social interactions within animals and, to some degree, humans. Social stressors and the absence of positive social interaction are associated with an increase in cardiovascular disorders and mood. Cardiovascular pathophysiology is mediated by behavioral and physical reactivity to stressors (Heinrichs et al., 2003; Steptoe et al., 2004). One of the common disorders of heart disease induced by social stressors includes a change in the heart rate and heart rate variability in both human and animal models were described (Grippo et al., 2007).

To the best of our knowledge, pharmacokinetic studies

are limited to a few, none addressing the involvement of taurine; (2-aminomethane e-sulfonic acid) or taurine is considered a conditionally essential nutrient and is a special amino acid containing sulfonate group without carboxyl group. Calcium modulation, antioxidation, salt conjugation, inflammation, osmoregulation, and membrane stabilization are numerous physiological functions of taurine (Pandya et al., 2017). As well as has different biological effects on the cardiovascular system, skeletal muscle, retina, liver, kidney, and nervous system (Chen et al., 2019) therefore taurine may have a valuable effect on the treatment of cardiovascular problems (Ibrahim et al., 2020) and liver disease (Makhova et al., 2019) primarily by lessening manufacture of reactive oxygen species (ROS). Taurine is also utilized to recover from exhaustion prior tobeforey (Wang et al., 2020). Heart attacks seem to be the most common illnesses worldwide, and they are the major cause of death in both developed and developing countries, hence health care centers must concentrate on identifying suitable protection and management programs (Miyajima et al., 2007). One researcher focused on taurine intake in healthy male human volunteers once they were given a single injection of 4 g taurine in a capsule formulation (Ghandforoush-Sattari et al., 2010). Several investigations, such as one in male Sprague Dawley rats after intravenous administration of 20 mg/kg taurine, have provided an initial anoncept of taurine pharmacokinetics (Tang et al., 2014) or oral administration of 30 or 300 mg/kg taurine (Sved et al., 2007) and also intravenous injection to beagle dogs (Yu et al., 2013) have been investigated. While, on the other hand, to the best of our knowledge no systematic investigation of dose-dependent intravenous is available. Therefore, this study aimed to investigate the pharmacokinetics of intravenous administration of different taurine doses, against arrhythmia induced by social isolation through electrocardiography (ECG), and the current research emphases on the possible amelioration roles of taurine on arrhythmic rats to reduce hazard effects on cardiac function.

MATERIALS AND METHODS

Experimental design

The rats used in this investigation were adult male albino rats that weighed between 250-300 gm and were 8-10 weeks old. In the animal house belonging to the Department of Biology, Faculty of Science, Zakho University, the animals were grown and housed in plastic cages, bedded with wood pellets in a room with a controlled temperature of 243oC. During the test, the animals were kept on a 12/12-hour light/dark schedule. The rats were fed regular laboratory chow and given a sufficient supply of water. Just before trial, the rats were given time to acclimate. Normal rats were used to record ECG as a control, and the rats were isolated for 14 days after recording ECG. After isolation, an ECG was recorded for 30 minutes preceding infusion.

Animal social isolation

The rats were maintained in stainless steel cages suspended from the ceiling, which were sized according to the recent protocol for the care and use of laboratory animals. During testing, the animals were conditioned to the housing amenities for fourteen days. Before initiating the ECG signal, body weights were obtained.

Animal preparation

The animal experimental procedures conformed to the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH) in the United States and was approved by the Animal Research Ethics Committee at the University of Zakho. An intravenous administration of ketamine and xylazine was used to anesthetize all of the rats. A 24-gauge cannula was inserted into a tail vein to provide Taurine intravenously. ECG needle electrodes were inserted in the forelimbs and left hind leg of rats mounted on a holding board. (MLA-136, Animal Bio Amp, AD Instruments, Sydney, Australia) and a digitizer (Powerlab 8/35, AD Instruments, Sydney, Australia) have been hasd to magnify the ECG signals. Labchart7 software (AD Instruments, Sydney, Australia) was being used to analyze the digitized ECG, which supplied an automatic collection of data on the heartbeat rate and a number of normal cycles. The drugs were injected in a syringe that was connected to an infusion pump for infusion (Cell point, Gaithersburg, USA).

Calculations of dose and dosing

Individual dosages were determined based on the most current weekly body mass and altered weekly to ensure all rats were at the same dose level (i.e. mg/kg/day). All dosages were administered volumetrically at a ratio of 10 mL/kg. The vehicle was given to the control group at the same dose volume as the treated animals.

Experimental observations

The viability of all the animals has checked, all animals were observed daily in their cages. All of the findings were documented. The clinical observation was carried out on the main test animals while they were being handled and weighed. Alteration in the skin, fur, eyes, and irregular respiratory patterns were some of the possible indications reported. Changes in movement, posture, and responsiveness to touching were also noted, as were stimulant movements, stereotypies (e.g., excessive grooming, repetitive circling), and strange behavior (e.g., self-mutilation, walking backward). Throughout the research, subjects' body weights were reported approximately twice. On day 1 and after social isolation, all test animals were weighed.

Statistical analysis

All results have been presented as a median with an interquartile range. The Kruskal-Wallis test was used to determine differences in all non-parametric variables, and Dunn's test was also used to correct the results, while one-way ANOVA has been used to compare the means of QRS among groups, followed by a Tukey post hoc test. All test statistics were two-tailed, and statistical significance was Prism 7 has been used to construct all graphs, calculations, and statistical considered as (P≤0.05). GraphPad analyses (GraphPad Software, San Diego, California, USA).

RESULTS

The inspection of the obtained data in Figure 1 were reported a significant (P < 0.001) decrease in body weight as a result of social isolation. The mean values recorded in socially isolated rats were 259.78 ± 34.43g. Social isolation was used to induce arrhythmias in male albino rats, which caused a non-significant increase in heart rate in comparison to control (283.4 ±90.9 control and 321.3±74.7 isolation, Table 1). Taurine at a dose of 1mg/kg/hr caused a non-significant decrease in heart rate. Further decrement in heart rate was reported when taurine at dose 2.5mg/kg/hr and 10mg/kg/hr was infused and similarly, the change was insignificant (320.3 ± 57.8, 314.6±88.4 and 324.3±82.8, respectively) as shown in (Table 1, Figure 2).

To evaluate the direct effect of taurine on JT intervals, doses of taurine infused and wait 10 min for each dose ECG was recorded and ECG changes were measured. After rat isolation JT intervals in comparison to control increased but did not show significant value. Further incensement was resulted after infusion of 1mg/kg/hr, 2.5mg/kg/hr and 10mg/kg/hr) taurine (0.046 ± 0.041, 0.052 ± 0.019, 0.05285 ± 0.021, 0.054 ± 0.026 and 0.059 ± 0.015), respectively, (Figure 3).

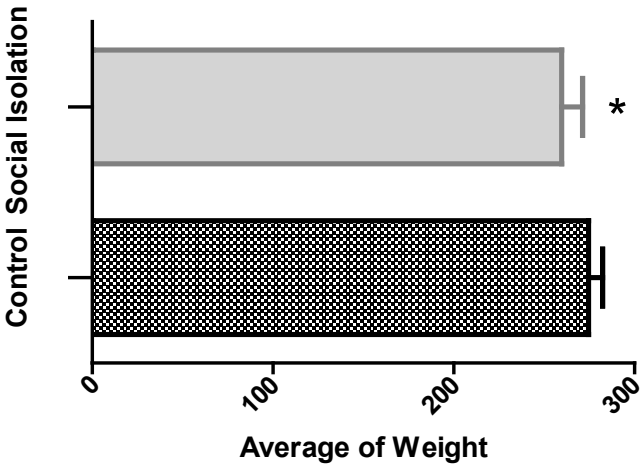

Figure 1: The effects of social isolation on rat weight in comparison to control. Data are expressed as Median ± interquartile range.

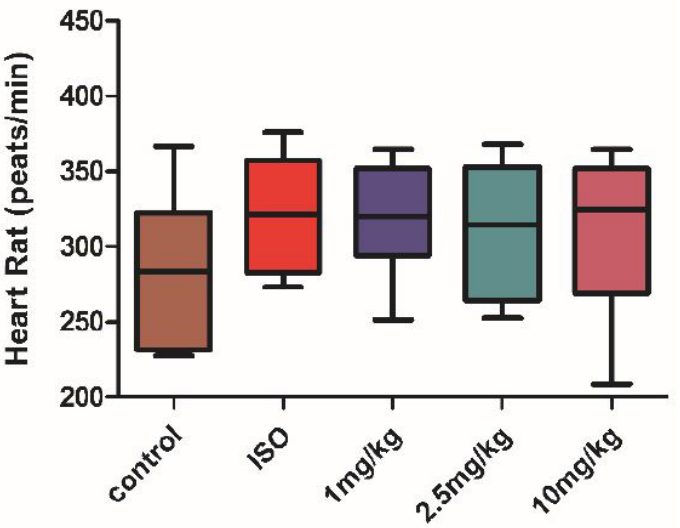

Figure 2: The effects of taurine infusion (1mg/kg, 2.5mg/kg, and 10mg/kg) on heart rate in Social isolation-induced cardiac arrhythmia in male albino rats. No significant difference was observed between the groups. Data are expressed as Median ± interquartile range.

Table 1: The effects of 1, 2.5, and 10mg/kg of Taurine infusion on some heart parameters (Median±interquartile range) in cardiac arrhythmia in male albino rats.

Parameter	control	Social Iso	1mg/kg	2.5mg/kg	10mg/kg
HR (BPM)	283.4 ±90.9	321.3±74.7	320.3 ± 57.8	314.6±88.4	324.3±82.8
RR Interval (s)	0.170±0.052	0.187±0.047	0.1874±0.036	0.191 ±0.057	0.186±0.053
PR Interval (s)	0.058±0.006	0.055±0.004	0.05733±0.009	0.058±0.006	0.059±0.006
QRS Interval (s)	0.018±0.004	0.017±0.007	0.01805±0.007	0.019±0.008	0.019±0.006
QT Interval (s)	0.065±0.037	0.073±0.021	0.07204±0.018	0.074±0.027	0.077±0.008
QTc Interval (s)	0.144±0.094	0.175±0.042	0.1653±0.036	0.167± 0.040	0.178±0.037
P Duration (s)	0.017±0.004	0.018±0.003	0.01765±0.005	0.017±0.005	0.017±0.004
P Amplitude(μV)	0.088±0.181	0.087±0.047	0.0973±0.0317	0.086±0.045	0.093±0.055
JT interval (s)	0.046±0.041	0.052±0.019	0.05285±0.021	0.054±0.026	0.059±0.015
ST Height (μV)	- 0.215± -1.631	0.032±0.046	0.03293±0.095	0.026±0.098	0.033±1.631

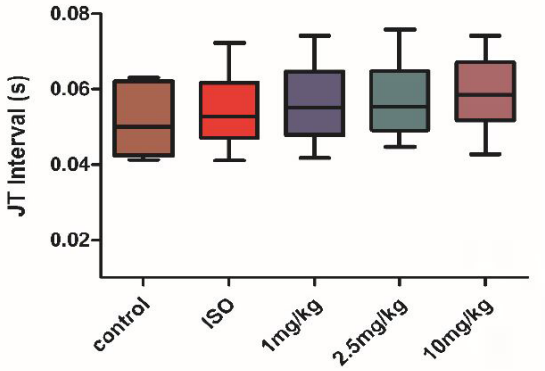

Figure 3: The effects of Taurine infusion (1mg/kg/hr, 2.5mg/kg/hr, and 10mg/kg/hr) on JT Interval in Social isolation-induced cardiac arrhythmia in male albino rats. No significant difference was observed between the groups. Data are expressed as Median ± Interquartile range.

Bazett's formula, a very useful tool to calculate QT which adjusted QT interval to HR. Which is based on dividing QT interval by square root of RR interval. In this research, social isolation and taurine dose-dependent change QT interval and insignificantly increase in comparison to control (0.065±0.037, 0.073±0.021, 0.07204±0.018, 0.074±0.027, and 0.077±0.008) respectively, (Figure 4). Similarly, the QTc parameter in this investigation changed and was reported to be (0.144±0.094 control vs isolation 0.175±0.042). Further increase was recorded when taurine dose (1mg/kg/hr, 2.5mg/kg/hr and 10mg/kg/hr) infused (0.1653±0.036, 0.167± 0.040, 0.178±0.037, respectively). Non-Significant changes of P amplitude, Q amplitude, R amplitude, S amplitude, and T Amplitude were recorded (Figures 4, 5, 6, 7, 8, respectively). The highest level of P amplitude was at control, for Q amplitude was at taurine (10mg/kg/hr). Meanwhile, S amplitude increase in social isolation rats. While T amplitude decrease in comparison to control.

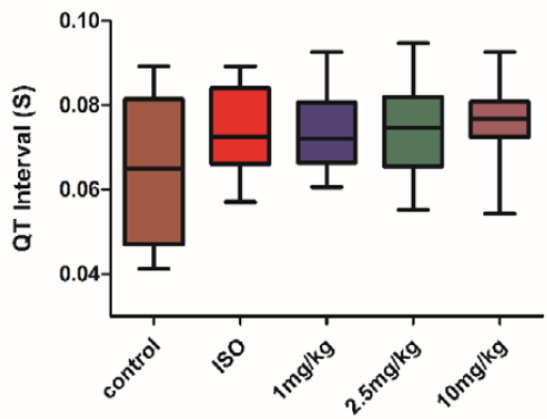

Figure 4: The effects of Taurine infusion (1mg/kg/hr, 2.5mg/kg/hr, and 10mg/kg/hr) on QT interval in Social isolation-induced cardiac arrhythmia in male albino rats. No significant difference was observed between the groups. Data are expressed as Median±interquartile range.

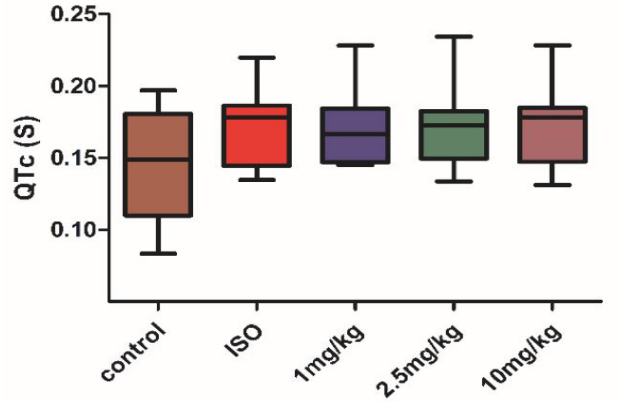

Figure 5: The effects of Taurine infusion (1mg/kg/hr, 2.5mg/kg/hr, and 10mg/kg/hr) on QTc interval in Social isolation-induced cardiac arrhythmia in male albino rats. No significant difference was observed between the groups. Data are expressed as Median ± interquartile range.

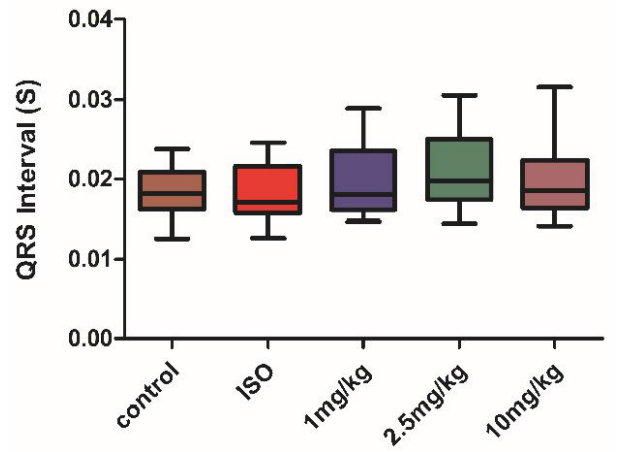

Figure 6: The effects of Taurine infusion (1mg/kg/hr, 2.5mg/kg/hr, and 10mg/kg/hr) on QRS interval in Social isolation-induced cardiac arrhythmia in male albino rats. No significant difference was observed between the groups. Data are expressed as Median ± interquartile range.

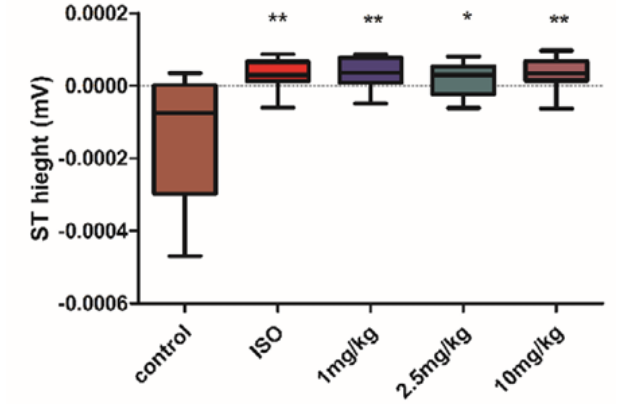

Figure 7: The effects of Taurine infusion (1mg/kg/hr, 2.5mg/kg/hr, and 10mg/kg/hr) on ST height in Social isolation-induced cardiac arrhythmia in male albino rats. A significant difference was observed between the groups. Data are expressed as Median ± interquartile range.

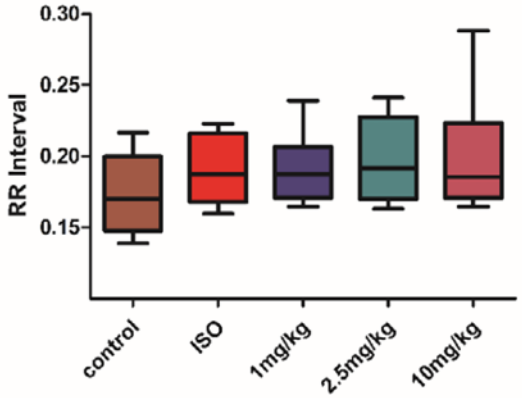

Figure 8: The effects of Taurine infusion (1mg/kg/hr, 2.5mg/kg/hr, and 10mg/kg/hr) on RR interval in Social isolation-induced cardiac arrhythmia in male albino rats. No significant difference was observed between the groups. Data are expressed as Median ± interquartile range.

Once rats were treated with 1mg/kg/hr, 2.5mg/kg/hr, and 10mg/kg/hr of taurine, the QRS complex, which reflects simultaneous stimulation of the right and left ventricles, was not significantly different from that of previous normal ECG recordings (0.018±0.004 control and 0.017±0.007 isolated rats) then little increase in the interval was reported after taurine treatment (0.01805±0.007, 0.019±0.008 and 0.019±0.006, respectively), as can be seen in (Figure 9).

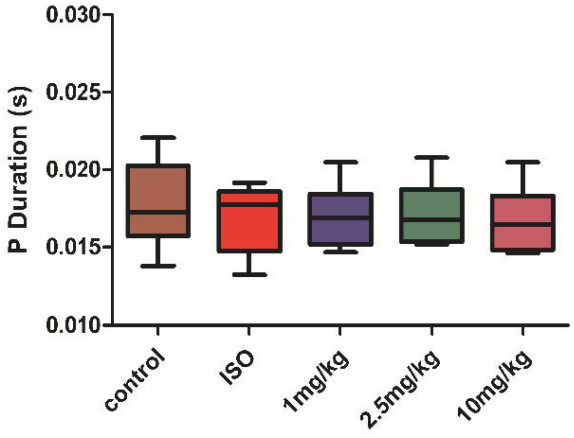

Figure 9: The effects of Taurine infusion (1mg/kg/hr, 2.5mg/kg/hr and 10mg/kg/hr) on P duration in Social isolation-induced cardiac arrhythmia in male albino rats. No significant difference was observed between the groups. Data are expressed as Median ± interquartile range.

The data from the current study indicated that ST intervals in comparison to control increased significantly (< 0.0001) after social isolation (-0.215± -1.63, 0.032±0.046), respectively. As well as, after taurine, infusion ST interval increase and the change at taurine 1 and 10 mg/kg/hr were highly significant, while, at taurine 2.5mg/kg/hr, the change was slightly significant when compared with control (0.03293±0.095 (1mg/kg/hr), 0.026±0.098 (2.5mg/kg/hr), and 0.033±1.631 (10 mg/kg/hr) (Table 1, Figure 10).

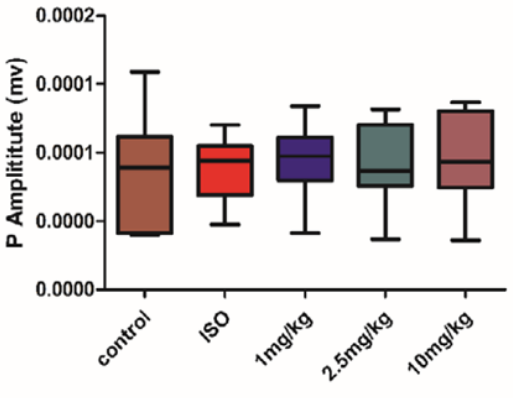

Figure 10: The effects of Taurine infusion (1mg/kg/hr, 2.5mg/kg/hr, and 10mg/kg/hr) on P amplitude in Social isolation-induced cardiac arrhythmia in male albino rats. No significant difference was observed between the groups. Data are expressed as Median ± interquartile range.

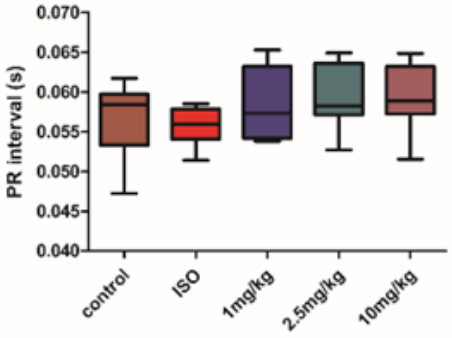

Figure 11: The effects of Taurine infusion (1mg/kg/hr, 2.5mg/kg/hr, and 10mg/kg/hr) on PR interval in Social isolation-induced cardiac arrhythmia in male's albino rats. No significant difference was observed between the groups. Data are expressed as Median ± interquartile range.

DISCUSSION

Cardiovascular disease remains a crucial and universal problem, greatly contributing to the world's leading causes of morbidity and mortality. In the present work, male albino rats Rattus rattus were socially isolated and then injected different doses of taurine to cause arrhythmia. This experiment revealed that social isolation resulted in a significant weightoss. This significant weight change may be due to a change in hormonal activity such as the Adrenocorticotropic hormone (ACTH), which plays a crucial role in response to stress. Presumably, change in ACTH (Perelló et al., 2006).

Hyper locomotion, which has been considered as a character for the so-called isolation syndrome (Heidbreder et al., 2000), is a consistent observation and early onset in isolation housed rats and can be detected by obvious means (Wongwitdecha and Marsden, 1996). Animals

raised locomotor behavior after 40 minutes of social isolation and for the rest of their lives, according to new research. Surprisingly, individuals who were isolated at the time of testing displayed usual hyperactivity regardless of age, implying that social isolation of ratthe s should be avoided if possible throughout life (Begni et al., 2021). Furthermore, it is clear from this study that when rats were socially isolated, the activity of cardiac function and heart rate increased, resulting in progressive cardiac responsiveness. Such clinical condition promotes the initiation of arrhythmia. These disturbances are common in heart disease, predicting mortality following myocardial infarction and heart failure (Grippo et al., 2003; Tapanainen et al., 2002). Previously, established that chronic stress causes behavioral and cardiovascular abnormalities in rats, which is handled in part by increased sympathetic drive, which leads to heart failure (Grippo et al., 2004).

In the current work, male albino rats Rattus rattus were socially isolated for 14 days to develop arrhythmia. After being treated with taurine, the isolated group showed higher HR, suggesting that isolation decreases vagal regulation of the heart (Grippo et al., 2007). Taurine caused a significant drop in heart rate, as evidenced by this study. The mechanism by which taurine lowers heart rate is thought to be related to an increase in Ca2+ sensitivity of muscle fibers, which changes tension production. Which were linked to the modification of sarcoplasmic reticular Ca2+ release, with the effect being less when the sarcoplasmic reticulum includes a high Ca2+ load and more when the sarcoplasmic reticulum contains a Ca2+ deficient sarcoplasmic reticulum (Schaffer et al., 2010). They observed that rats given a taurine transporter blocker had a longer contractile cycle by decreasing Ca2+ clearance from the cytosol, indicating that taurine deficit is linked to a decrease in heart muscle sensitivity to Ca2+. The phosphorylation of troponin I in the heart has been found to be considerably increased in taurine transporter knockout mice. Because phosphorylation of troponin I inhibits the coupling of Ca2+ to troponin C, it limits tension production (Schaffer et al., 2009).

Data from the echocardiographic analysis revealed that the cardiomyopathy created by taurine deficiency was attributed to reduced fractional shortening combined with an increase in left ventricular chamber dimensions and impaired response to dobutamine and also supporting that rodents, when genetically taurine transporter abolished, taurine deficient cardiomyopathy was developed (Ito et al., 2008). Taurine might be linked through some mechanism to the workload of the heart. Diminished handling of calcium by the heart, impaired calcium sensitivity of the contractile proteins, loss of cardiomyocytes, and insufficient ATP to drive contraction, are such clinical conditions that promote the initiation of cardiac diseases such as heart failure and some of these conditions are taurine dependent (Ibrahim et al., 2020; Schaffer et al., 2010).

Recently, the investigation indicated that in rats treated with a salt diet increased blood pressure then after being treated with taurine blood pressure returned to normal (Schaffer et al., 2010). Similarly, Novotny and his colleagues in 1991 found in cat's increment in ventricular chamber compliance and decreases in the rate of pressure rise in the taurine deficient heart and illustrated that taurine act as a free radical scavenger (Novotny et al., 1991). After administration of taurine function of endothelin nitric oxide synthesis increased, causing an enhancement of nitric oxide activity and a diminishing of O2 and ONOO generation (Touyz and Schiffrin, 2001). Because increasing production of reactive oxygen species induced oxidative stress (Grossman, 2008), which consider the main hazard for cardiovascular sickness and death in industrialized and poor countries. Since oxidative stress is recognized to cause intracellular Ca+2 overload, the variation of Ca+2 ion by taurine may probably be intermediated via its antioxidant effects. Further mechanisms described by several clinical and experimental researches about the taurine role in protecting the cardiovascular system such as an improved lipid profile and antagonism of angiotensin II action (Kaneyuki et al., 2007; Ulrich-Merzenich et al., 2007). Few studies found that drug-induced taurine deficiency enhances angiotensin II-mediated apoptosis (Schaffer et al., 2003).

Furthermore, the current result indicated that elevation in the taurine concentration, increase heart function, this may be due to enhances Na+-Ca2+ exchange activity and elevates [Ca2+] i., as well as, affect the transport of other ions the fast Na+ current and Cl current (Schaffer et al., 2000). Previously, it is published that electrical activation of the heart and duration of QT/QTc interval are dependent on nitric oxide (Atabay and Uzun, 2009). While, data from the current study revealed non-significant changes of both JT, QT intervals, and QTc which means ventricular repolarization cannot be changed by NO. This result was emphasized by (Wang et al., 2003), he was indicated that for maintaining hemodynamics basal NO is important but shows a limited impact on ventricular repolarization.

The data of the current study illustrated little decrement in the P and PR amplitude after social isolation then little increment after being treated with taurine which indicated that may taurine and NO had a small effect on the depolarization of the right atrium (Chowdhary et al., 2020). The end of the deflection developed by depolarization of the ventricles and the starting of the deflection produced by repolarization of the ventricles, also known as the S-T segment, shows a sudden alteration in the length amplitude after social isolation and after a high

dose of taurine could represent a flow and requirement in the myocardium are at their maximum.

CONCLUSION

This work uses an integrative approach to investigate heart rhythm in a socially isolated rat model system, which is then treated with taurine. Both affective and cardiovascular diseases are triggered by social isolation. These findings show how taurine affects rat behavior and physiology.

ACKNOWLEDGMENT

We thank members of the Biology Department, Faculty of Science, Zakho University for their technical support and providing ECG Bio-Amplifier.

NOVELTY STATEMENT

This research is the first to emphases on the possible roles of taurine on arrhythmic rats to reduce hazard effects on cardiac function.

AUTHOR'S CONTRIBUTION

Chinar Mustafa Mohammad designed, coordinated, analyzed the data, and wrote the manuscript. Omar A.M. Al-Habib supervised and revised the manuscript. Mohammed Bassam, Thamer M. Bashir, and Farhad Ramadhan collected the data. All authors read and approved the final version of the manuscript.

Conflict of interest

The authors have declared no conflict of interest.

REFERENCES

Atabay T, Uzun M (2009). The correlation between the plasma nitric oxide levels and QT/QTc interval in conscious rabbits. Gen. Physiol. Biophys., 28(1): 16–23. https://doi.org/10.4149/gpb_2009_01_16

Begni V, Sanson A, Pfeiffer N, Brandwein C, Inta D, Talbot SR, Mallien AS (2021). Correction: Social isolation in rats: Effects on animal welfare and molecular markers for neuroplasticity. PLoS One, 16(2): e0248070. https://doi.org/10.1371/journal.pone.0248070

Chen C, Xia S, He J, Lu G, Xie Z, Han H (2019). Roles of taurine in cognitive function of physiology, pathologies and toxication. Life Sci., 231: 116584. https://doi.org/10.1016/j.lfs.2019.116584

Chowdhary S, Harrington D, Bonser RS, Coote JH, Townend JN (2020). Chronotropic effects of nitric oxide in the denervated human heart. J. Physiol., 541(Pt 2): 645–651. https://doi.org/10.1113/jphysiol.2001.015107

Durham D, Worthley LI (2002a). Cardiac arrhythmias: Diagnosis and management. The bradycardias Critical care and resuscitation. J. Austral. Acad. Crit. Care Med., 4(1): 35-53.

Ghandforoush-Sattari M, Mashayekhi S, Krishna CV, Thompson JP, Routledge PA (2010). Pharmacokinetics of oral taurine in healthy volunteers. J. Amino Acids, 2010: 346237. https://doi.org/10.4061/2010/346237

Grippo AJ, Beltz TG, Johnson AK (2003). Behavioral and cardiovascular changes in the chronic mild stress model of depression. Physiol. Behav., 78(4-5): 703–710. https://doi.org/10.1016/S0031-9384(03)00050-7

Grippo AJ, Lamb DG, Carter CS, Porges SW (2007). Social isolation disrupts autonomic regulation of the heart and influences negative affective behaviors. Biol. Psychiatry, 62(10): 1162–1170. https://doi.org/10.1016/j.biopsych.2007.04.011

Grippo AJ, Santos CM, Johnson RF, Beltz TG, Martins JB, Felder RB, Johnson AK (2004). Increased susceptibility to ventricular arrhythmias in a rodent model of experimental depression. Am. J. Physiol. Heart Circul. Physiol., 286(2): H619–H626. https://doi.org/10.1152/ajpheart.00450.2003

Grossman E (2008). Does increased oxidative stress cause hypertension? Diabetes Care, 31(Suppl 2): S185–S189. https://doi.org/10.2337/dc08-s246

Heidbreder CA, Weiss IC, Domeney AM, Pryce C, Homberg J, Hedou G, Nelson P (2000). Behavioral, neurochemical and endocrinological, characterization of the early social isolation syndrome. Neurosci., 100(4): 749–768. https://doi.org/10.1016/S0306-4522(00)00336-5

Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U (2003). Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biol. Psychiatry, 54(12): 1389–1398. https://doi.org/10.1016/S0006-3223(03)00465-7

Ibrahim MA, Eraqi MM, Alfaiz FA (2020). Therapeutic role of taurine as antioxidant in reducing hypertension risks in rats. Heliyon, 6(1): e03209. https://doi.org/10.1016/j.heliyon.2020.e03209

Ito T, Kimura Y, Uozumi Y, Takai M, Muraoka S, Matsuda T, Azuma J (2008). Taurine depletion caused by knocking out the taurine transporter gene leads to cardiomyopathy with cardiac atrophy. J. Mol. Cell. Cardiol., 44(5): 927-937. https://doi.org/10.1016/j.yjmcc.2008.03.001

Kaneyuki U, Ueda S, Yamagishi S, Kato S, Fujimura T, Shibata R, Okuda S (2007). Pitavastatin inhibits lysophosphatidic acid-induced proliferation and monocyte chemoattractant protein-1 expression in aortic smooth muscle cells by suppressing Rac-1-mediated reactive oxygen species generation. Vasc. Pharmacol., 46(4): 286–292. https://doi.org/10.1016/j.vph.2006.11.002

Makhova AA, Shikh EV, Bulko TV, Sizova ZM, Shumyantseva VV (2019). The influence of taurine and L-carnitine on 6 β-hydroxycortisol/cortisol ratio in human urine of healthy volunteers. Drug Metab. Pers. Ther., 34(3): 10.1515/dmpt-2019-0013. https://doi.org/10.1515/dmpt-2019-0013

Miyajima K, Minatoguchi S, Ito Y, Hukunishi M, Matsuno Y, Kakami M, Fujiwara H (2007). Reduction of QTc dispersion by the angiotensin II receptor blocker valsartan may be related to its anti-oxidative stress effect in patients with essential hypertension. Hypertens. Res. Off. J. Japanese Soc. Hypertension, 30(4): 307-313. https://doi.org/10.1291/hypres.30.307

Novotny MJ, Hogan PM, Paley DM, Adams HR (1991). Systolic and diastolic dysfunction of the left ventricle

induced by dietary taurine deficiency in cats. Am. J. Physiol., 261(1 Pt 2): H121–H127. https://doi.org/10.1152/ajpheart.1991.261.1.H121

Pandya K, Clark GJ, Lau-Cam CA (2017). Investigation of the role of a supplementation with taurine on the effects of hypoglycemic-hypotensive therapy against diabetes-induced nephrotoxicity in rats. Adv. Exp. Med. Biol., 975(Pt 1): 371–400. https://doi.org/10.1007/978-94-024-1079-2_32

Perelló M, Chacon F, Cardinali DP, Esquifino AI, Spinedi E (2006). Effect of social isolation on 24-h pattern of stress hormones and leptin in rats. Life Sci., 78(16): 1857–1862. https://doi.org/10.1016/j.lfs.2005.08.029

Schaffer SW, Azuma J, Mozaffari M (2009). Role of antioxidant activity of taurine in diabetes. Can. J. Physiol. Pharmacol., 87(2): 91-99. https://doi.org/10.1139/Y08-110

Schaffer SW, Jong CJ, Ramila KC, Azuma J (2010). Physiological roles of taurine in heart and muscle. J. Biomed. Sci., 17(Suppl 1): S2. https://doi.org/10.1186/1423-0127-17-S1-S2

Schaffer SW, Solodushko V, Pastukh V, Ricci C, Azuma J (2003). Possible cause of taurine-deficient cardiomyopathy: potentiation of angiotensin II action. J. Cardiovasc. Pharmacol., 41(5): 751–759. https://doi.org/10.1097/00005344-200305000-00012

Schaffer SW, Takahashi K, Azuma J (2000). Role of osmoregulation in the actions of taurine. Amino Acids, 19(3-4): 527–546. https://doi.org/10.1007/s007260070004

Steptoe A, Owen N, Kunz-Ebrecht SR, Brydon L (2004). Loneliness and neuroendocrine, cardiovascular, and inflammatory stress responses in middle-aged men and women. Psychoneuroendocrinology, 29(5): 593–611. https://doi.org/10.1016/S0306-4530(03)00086-6

Sved DW, Godsey JL, Ledyard SL, Mahoney AP, Stetson PL, Ho S, Renwick AG (2007). Absorption, tissue distribution, metabolism and elimination of taurine given orally to rats. Amino acids, 32(4): 459–466. https://doi.org/10.1007/s00726-007-0494-3

Tang DQ, Bian TT, Zheng XX, Li Y, Wu XW, Li YJ, Jiang SS (2014). LC-MS/MS methods for the determination of edaravone and/or taurine in rat plasma and its application to a pharmacokinetic study. Biomed. Chromatogr. BMC, 28(9): 1173–1182. https://doi.org/10.1002/bmc.3139

Tapanainen JM, Thomsen PE, Køber L, Torp-Pedersen C, Mäkikallio TH, Still AM, Huikuri HV (2002). Fractal analysis of heart rate variability and mortality after an acute myocardial infarction. Am. J. Cardiol., 90(4): 347–352. https://doi.org/10.1016/S0002-9149(02)02488-8

Touyz RM, Schiffrin EL (2001). Increased generation of superoxide by angiotensin II in smooth muscle cells from resistance arteries of hypertensive patients: Role of phospholipase D-dependent NAD(P)H oxidase-sensitive pathways. J. Hypertens., 19(7): 1245–1254. https://doi.org/10.1097/00004872-200107000-00009

Ulrich-Merzenich G, Zeitler H, Vetter H, Bhonde RR (2007). Protective effects of taurine on endothelial cells impaired by high glucose and oxidized low density lipoproteins. Eur. J. Nutr., 46(8): 431–438. https://doi.org/10.1007/s00394-007-0682-7

Wang, El-Kebir D, Blaise G (2003). Inhaled nitric oxide in 2003: a review of its mechanisms of action. Can. J. Anaesth. J. Can. D'anesth., 50(8): 839–846. https://doi.org/10.1007/BF03019384

Wang-Ma N, He F, Kawanishi S, Kobayashi H, Oikawa S, Murata M (2020). Taurine Attenuates Carcinogenicity in Ulcerative Colitis-Colorectal Cancer Mouse Model. Oxidative med. Cell. Longevity, 2020: 7935917. https://doi.org/10.1155/2020/7935917

Wongwitdecha N, Marsden CA (1996). Social isolation increases aggressive behaviour and alters the effects of diazepam in the rat social interaction test. Behav. Brain Res., 75(1-2): 27–32. https://doi.org/10.1016/0166-4328(96)00181-7

Yousry SM, Taha RAM, El-Banna HA, Emam SR (2021). Curative and protective effect of salvia officinalis oil on isoprenaline-induced congestive heart failure in rats. Adv. Anim. Vet. Sci., 9(11): 1895-1907. https://doi.org/10.17582/journal.aavs/2021/9.11.1895.1907

Yu YY, Zheng XX, Bian TT, Li YJ, Wu XW, Yang DZ, Tang DQ (2013). Development and application of a LC-MS/MS assay for the simultaneous quantification of edaravone and taurine in beagle plasma. J. Sep. Sci., 36(24): 3837–3844. https://doi.org/10.1002/jssc.201300983