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Chronic Administration of Monosodium Glutamate Induced Changes on Some Blood Electrolytes And Heart Enzymes in Male Sprague Dawley Rats

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Abstract

This study evaluated the chronic administration of Monosodium Glutamate to ascertain its effect/impact on blood electrolytes and some biomarkers of the heart, such as lactate dehydrogenase, Troponin and Creatine Kinase. Acclimatized Male Sprague-Dawley Rats (n=40) were randomly selected and grouped into four: Control(A), 3% LD50 (500mg/kg) (B), 12% LD50 MSG (2000mg/kg) (C) and 24% LD50 MSG (4000mg/kg) (D), and were orally administered MSG for 60 days. After the experimental period, blood samples were collected from the animals, activities of the biomarkers of the heart were evaluated, lipid peroxidation markers (MDA), oxidative stress marker enzymes: SOD, CAT, GSH were also evaluated. During the administration of the extract at various doses, heart enzymes showed significant decrease ($P< 0.05$) in rats which received 2000mg/kg and 4000mg/kg of Monosodium Glutamate when compared with the untreated group. Also, blood electrolytes and antioxidant enzymes showed significant decrease.

Monosodium Glutamate (MSG) from the result of this study can be said, when administered from 2000 and 4000mg/kg to lead to distortion and dilation of the tissues of the heart/ biomarkers of the heart.

Keywords: Monosodium Glutamate, Lactate Dehydrogenase, Troponin, Creatine Kinase, Antioxidants

INTRODUCTION

The heart has an important role in pumping blood throughout the body. It is crucial for delivering oxygen and nutrients and removing waste products. The heart's pumping action is essential for the body's overall health and survival (López-Miranda et al., 2015).

The use of MSG has been established, but studies have shown potential toxic effects. These effects include CNS disorders, obesity, liver harm, and impairments in reproductive function. If more evidence were presented regarding the toxicity of MSG, it would be wise to consider prohibiting its use. (Bautista *et al*., 2019; Brosnan *et al*., 2014)

Consumption of MSG has been associated with symptoms like headaches, allergies, and neurotoxicity. Concerns persist about its negative effects on human health, especially the heart. Research has also linked MSG consumption to obesity. However, the impact of long-term MSG exposure on the heart in adult male wistar rats has not been thoroughly studied (Bautista *et al*., 2019). Therefore, the objectives of this study are to determine the effects of MSG on blood electrolytes, biomarkers, antioxidant activity, lipid peroxidation, and histology of the heart tissues in adult male wistar rats. This research will provide insight into the potential effects of MSG on the human body and may inform strategies to prevent or manage its adverse effects. Furthermore, the use of animal models in this study lays the foundation for future research on human subjects. Thus, this research is crucial in advancing our understanding of the body's physiological and biochemical responses to dietary components and their implications for health.

MATERIALS AND METHOD

Reagent and Chemicals

MSG (Ajinomoto CO INC., Tokyo. Japan), phosphate buffer (pH 7.4, 0.1 M) (Oxford laboratories, Mumbai India), bluing solution, glacial acetic acid, hydrochloric acid (HCl), Haematoxylin and eosin staining, ellman reagent, gluthathion acid, thiobarbituric acid, carbonate buffer, analytical glucose (Oxford laboratories, Mumbai India), Distilled water, Methylated sprit, all other chemical used in this experiment were of analytical grade.

Ethical Approval

The National Institutes of Health's (2011) guidelines for the care and use of laboratory animals in research were followed in all animal experiments and methodology. The Olabisi Onabanjo University Teaching Hospitals Health Research Ethics Committee (OOUTH-HREC), with approval number OOUTH/HREC/669/2023AP, granted ethical clearance.

Preparation of Monosodium Glutamate

The doses of MSG used for this study is determined from the LD_{50} of monosodium glutamate which is 16,600mg/kg (Walker and Lupien, 2000). A solution of 10 grammes of MSG (ratio 1g to 100ml) was made in 100 milliliters of distilled water. 500 mg, 2000 mg and 4000 mg of MSG/ Body weight of rats, was obtained from the stock solution according to the method described by Erhirhie *et*

al., (2014), using the formula:

$$\frac{Dose\ rate\ x Body\ Weight}{Stock\ Concentration}$$

Experimental Design and Treatment

In this experiment, we utilized forty healthy Adult male Sprague-Dawley rats, each weighing 70g to 100g. The rats were given a period of fourteen days to acclimatize to their surroundings during which they were provided with a standardized pellet diet and unrestricted access to water. After the acclimatization period, the rats were weighted and randomly divided into four groups, each consisting of 10 rats, Group A served as the control, they received water only, Group B exposed to 3% of LD50, received a daily dosage of 500mg/kg of MSG via oral gavage, Group C, subjected to 12% LD50 received a daily dosage of 2000mg/kg of MSG through oral gavage. Lastly, Group D, exposed to 24% LD50, received a daily dosage of 4000mg/kg of MSG via oral gavage. The animals were housed at ambient temperature ranging from 20 - 25ºC and humidity of 40-45% with a 12-hour light-dark schedule at the animal house, Obafemi Awolowo College of Health Sciences, Sagamu, Ogun State, Nigeria. The rats were placed on pelleted diet and water *ad libitum* during the period of acclimatization and throughout the period of the experiment. The administration of MSG was carried out daily for a total duration of sixty days.

Animal Sacrifice and Collection of Blood Samples

The animals were euthanized by cervical dislocation 6 hours after the completion of the study. The targeted organ, the heart, was removed through a midline incision in the abdomen and weighed in relation to the body weight. Blood was obtained from the orbital sinus under mild ether anesthesia, with the rats gently restrained and their necks gently scratched to promote eye protrusion. A capillary tube was inserted into the eye and blood was collected into a bottle containing EDTA (Ethylenediamine tetra acetic acid) bottle.

Biochemical Analysis: Determination of Antioxidant activities

In the Heart, SOD activity were determined by the method of Misra and Fridovich (1972), CAT activity were determined by the method of Sinha (1972), while GSH activity was determined by the method of Sedlak and Lindsay (1968), and Jollow et al. (1974). The MDA activity of the Heart was determined using the methods of Stocks and Dormandy (1971).

Statistical Analysis

All the values are expressed as mean ± standard error of mean (SEM). Analysis of data was done using GraphPad Prism version 5 for Windows. Differences between groups were analyzed by one-way ANOVA followed by Dunnet *post-hoc* test. Differences were considered significant when $P < 0.05$

RESULTS AND DISCUSSION

Results

Table 1: Lactate Dehydrogenase, Creatine Kinase and Troponin Activities in the Heart Tissue of Adult Male Sprague-Dawley Rats During Administration of Monosodium Glutamate.

Group	Lactate Dehydrogenase (u/l)	Creatine Kinase (u/l)	Troponin I (pg/ml)
A	212.9 ± 7.704	18.12 ± 0.98	156.5 ± 2.379
B	195.9 ± 4.085[a]	32.75 ± 2.354	102.9 ± 1.602[a]
C	124.3 ± 3.103[a]	4.93 ± 0.49[a]	64.65 ± 5.555[a]
D	38.45 ± 7.886[a]	9.86 ± 0.98[a]	20.86 ± 5.267[a]

[a:] shows statistical significance at $P < 0.05$ when compared with the control group (Group A)

Table 1 shows the result of long-term MSG Exposure on heart enzymes in adult male Sprague-Dawley Rats. The graph shows that Monosodium Glutamate Exposure at doses of 500mg/kg, 2000mg/kg and 4000mg/kg for sixty days caused a statistical decrease in lactate dehydrogenase when compared with the control group. Lactate Dehydrogenase is involved in converting lactate to pyruvate in the body, which is used for energy. It is found in various tissues and organs and is tested for tissue damage. Lactate Dehydrogenase levels can change due to different conditions. (Diniz *et al*., 2004)

When Lactate Dehydrogenase Activity is high, it can indicate various health conditions. When Lactate Dehydrogenase Activity is low, it can be caused by liver disease, malnutrition, and certain medications. The exact way MSG reduces Lactate Dehydrogenase levels is not fully understood, but it is believed to affect glutamate receptors in the heart. Dietary changes can affect LDH levels. Some food seasonings have been linked to negative health effects, as shown in the table where group C and D decreased significantly compared to the control group. This implies that the animals would likely be unable to sustain life and function properly. The problems that may arise as a result of this includes diabetes and metabolic disorders. These conditions often involve a disruption in the body's ability to convert food into energy leading to a range of health issues.

The table shows that MSG exposure at dose of 500mg/kg causes a significant increase in creatine kinase levels when compared with the control group; Exposure at doses of 2000mg/kg and 4000mg/kg for 60 days causes a statistical decrease in creatine levels when compared with the control group.

Creatine Kinase is an enzyme found in the heart, brain, and skeletal muscle and its high levels in the blood may indicate heart muscle damage. Elevated levels of CK-MB can suggest heart muscle damage and cardiac issues. A decrease in CK level may indicate a decrease in the enzyme's activity or presence in the heart muscles (Vonk-Noordegraaf *et al*., 2013)

Exposure to MSG at different doses caused a decrease in Troponin level activity. Troponin is a protein found in muscle tissues, especially in the heart, and elevated levels can indicate heart damage. Fluctuations in troponin level can suggest myocardial injury or infarction, which is a major

health problem causing reduced blood flow to the heart. There isn't enough evidence to directly link MSG to changes in troponin levels (Insawang *et al*., 2012)

Table 2: Potassium, Chloride, Sodium and Bicarbonate Level During the Administration of Monosodium Glutamate in Adult Male Sprague-Dawley Rats.

Blood Electrolyte (mmol/L)	GroupA (Distilled Water and feed only)	GroupB (500mg/kg)	GroupC (2000mg/kg)	GroupD (4000mg/kg)
K^+	7.40 ± 1.50	6.65 ± 0.25[a]	7.60 ± 0.20	6.40 ±0.50[a]
Cl^-	73.00 ± 23.00	75.00 ± 20.00	75.50 ± 18.50	78.50 ± 23.50
Na^+	166.5 ± 23.50	164.00 ± 16.00[a]	172.50 ± 27.50	161.50± 28.50[a]
$HCO3^-$	12.00 ± 3.10	7.10 ± 0.20[a]	8.30± 0.50[a]	9.15 ± 2.25[a]

[a]: shows statistical significance at P< 0.05 when compared with the control group (Group A)

Table 2 shows evaluation of blood electrolytes during the administration of monosodium glutamate in adult male Sprague Dawley Rats; Potassium is the major cation of the intracellular fluid and it has decreased concentration in extracellular fluid. Some roles of potassium are the regulation of heartbeat and muscle function. It aids establishing the resting membrane potential in neurons and muscle fibers after membrane depolarization and action potentials. The proper level of potassium is essential for normal body function. Any seriously abnormal increase or decrease in potassium can profoundly affect the nervous system and increase change in irregular heartbeat (Mocliandari *et al*., 2002).

Hypokalemia is a decrease in blood potassium level, caused by redistribution or absolute decrease of potassium. Hyperkalemia can occur from excess dietary potassium intake, leading to high concentrations in the ECF. High potassium levels in the blood can cause the heart to seize and stop pumping, resulting in death within minutes (Onyema *et al*., 2006).

Observation from the result of the analysis showed that there was a statistical decrease in Potassium level in Group B (6.65 ± 0.25) and D (6.40 ± 0.50) when compared with Group A (7.40 ± 1.50). This decrease suggests that Monosodium Glutamate Administration at high dose would lead to muscle weakness, fatigue and irregular heart rhythms; severe cases may cause paralysis or life-threatening cardiac arrhythmias (Abnormal Heart Rhythms), this can alter the balance of electrolytes in the heart affecting its electrical signals. This imbalance may lead to irregular heartbeats, palpitations, or more serious arrhythmias.

However, there was a significant increase in Potassium level in the rats given the dose of 20000mg/kg of MSG in Group C (7.60 ± 0.20) when compared with Group A (7.40 ± 1.50). This increase can damage the role of skeletal muscle, the nervous system and the heart. It can lead to heart palpitations or even cardiac arrest.

Chloride is primarily found in the extracellular fluid and blood, and its levels are tightly regulated by the body. It helps maintain fluid balance (Mocliandari *et al*., 2002).

Hypochloremia can result from impaired renal tubular absorption, diarrhea, or metabolic acidosis.

Hyperchloremia can occur due to excessive salt intake, thirst, aspirin intoxication, congestive heart failure, or cystic fibrosis (Onyema *et al*., 2006).

Observation from the results of the analysis shows a statistical increase in Group B (75.00 ± 20.00), C (75.50 ± 18.50) and D (78.50 ± 23.50) when compared with Group A (73.00 ± 23.00). This increase suggests that Monosodium Glutamate Administration would lead to dehydration, congestive heart failure and the hereditary chronic lung disease, cystic fibrosis. There would be increased blood pressure and potential acid-base imbalances.

Hyponatremia refers to lower-than-normal sodium concentration due to excess water in the body. A decrease in sodium can occur from decreased intake and continuous excretion in urine. Sodium loss can also result from conditions like excessive sweating or vomiting (Mocliandari *et al*., 2002). Relative decrease in sodium can occur from sodium imbalance in other body fluids or water retention related to edema or congestive heart failure (Onyema *et al*., 2006).

Observation from the results showed that there was a significant decreased in sodium level in Group B (164.00 ± 16.00) and D (161.50 ± 28.50) when compared with Group A (166.5 ± 23.50). This decrease suggests that administration of monosodium glutamate at doses of 2000mg/kg and 4000mg/kg could causes nausea, headache, confusion, seizures and in several cases, it may lead to death or coma. Hyponatremia is often associated with conditions such as heart failures, kidney disorders or excessive fluid intake

Observation from the results also showed that there was a significant increase in sodium level in Group C (172.50 ± 27.50) when compared with Group A (166.5 ± 23.50). This increase suggests elevated level of sodium in the blood and its effect may include thirst, dry mucous membranes, restlessness, and in severe cases, confusion, seizures, or coma.

Bicarbonate is the second most abundant anion in the blood and acts as a buffer to maintain normal acidity (Mocliandari *et al*., 2002). Bicarbonate ions are produced from CO2 and water during aerobic metabolism (Onyema *et al*., 2006). Metabolic alkalosis occurs when there is an increase in bicarbonate levels in the blood, leading to symptoms such as muscle twitching and hand tremors. Metabolic acidosis occurs when there is a decrease in bicarbonate levels, resulting from conditions such as kidney dysfunction or severe diarrhea, and can cause symptoms such as rapid breathing and confusion.

Observation from HCO_3^- (Bicarbonate level) showed a significant decrease in Group B (7.10 ± 0.20), C (8.30 ± 0.50) and D (9.15± 2.25). This decrease suggests that the body is either producing too much acid or losing too much bicarbonate. Metabolic acidosis can be caused by various factors, including kidney dysfunction, uncontrolled diabetes, severe diarrhea, or ingestion of certain toxins. The results of low level of bicarbonate includes, rapid breathing, confusion, cardiac issues, nausea and vomiting and it can also lead to shock.

Table 3: Glutathione, Superoxide Dismutase, Catalase and Malonaldehyde Level (Lipid Peroxidation) During the Administration of Monosodium Glutamate in Heart Tissues in Adult Male Sprague-Dawley Rats.

Groups	GSH (µmol/ml)	SOD (µmol/ml/min/mg pro)	CAT (µmol/ml/min/mg/pro)	MDA (µmol/ml)
A	15.01 ± 0.77	3.91 ± 0.37a	16.47 ± 1.44	3.60± 0.07[a]
B	18.03 ± 1.16	4.00 ± 0.57a	12.87 ± 1.39[a]	3.49 ± 0.55[a]
C	20.74 ± 0.15	4.78 ± 0.08a	19.34± 0.39[a]	2.85 ± 0.14[a]
D	17.95 ± 0.31	4.99 ± 0.35a	16.13± 4.17[a]	3.07± 0.26[a]

[a] : shows statistical significance at P< 0.05 when compared with the control group (Group A)

Table 3.3 shows evaluation of monosodium glutamate administration on antioxidant level and level of lipid peroxidation; Glutathione (GSH), a tripeptide that is ubiquitously present in cells, exhibits remarkable antioxidant properties, thereby shielding cells from the deleterious impact of free radicals. These unstable molecules possess the capability to inflict damage upon DNA, proteins, and lipid (Noftall *et al*., 2016).

Observations from the results shows a significant increase in Group B (18.03 ± 1.16), C (20.74 ± 0.15), and D (17.95 ± 0.31), when compared with the control group.

Increase in Glutathione level suggests that there could be allergic reactions, leading to symptoms such as rash, itching and difficulty in breathing; there could also be Gastrointestinal issues.

Superoxide Dismutase is crucial for protecting cells from the damaging effects of superoxide radicals. These extremely reactive substance has the capacity to damage lipids, proteins, and DNA (Petersson *et al*., 2005).

Observation from the result shows a significant increase in Group B (4.00± 0.57), C (4.78± 0.08) and D (4.99 ± 0.33) when compared with Group A (3.91± 0.37).

Catalase (CAT) is an enzyme that plays an important role in cellular defense against the harmful effects of hydrogen peroxide, a highly reactive molecule capable of causing impairment to DNA, proteins, and lipids (Onyema *et al*., 2006).

Observations from the result showed a significant decrease in Group B (12.87± 1.39) and D (16.13 ± 4.17), when compared with Group A (16.47± 1.44). This result suggests that a decrease in catalase levels suggests a potential reduction in the body's ability to efficiently neutralize hydrogen peroxide and other reactive oxygen species; catalase plays a crucial role in breaking down hydrogen peroxide into water and oxygen, thereby preventing oxidative damage to cells. A decline in catalase activity could result in an accumulation of hydrogen peroxide, leading to increased oxidative stress.

However, there was a significant increase in Group C (19.34± 0.39) when compared with group A (16.47±1.44). Elevated catalase level can indicate that the body is actively working to counteract higher level of oxidative stress. This may occur in occur in response to various factors such as exposure to environmental toxins, inflammation, or other stressors that lead to increased production of reactive oxygen species.

Malondialdehyde (MDA) is a compound that arises as a consequence of lipid peroxidation, a process characterized by the damage inflicted upon lipids, which constitute a major component of cell membranes, by free radicals. MDA serves as an indicator or marker for the occurrence of oxidative stress (Malik et al., 2013).

Observations from the results showed a significant decrease in Group B (3.49± 0.55), C (2.85±0.14) and Group D (3.07± 0.26) when compared with Group A (3.60± 0.07).

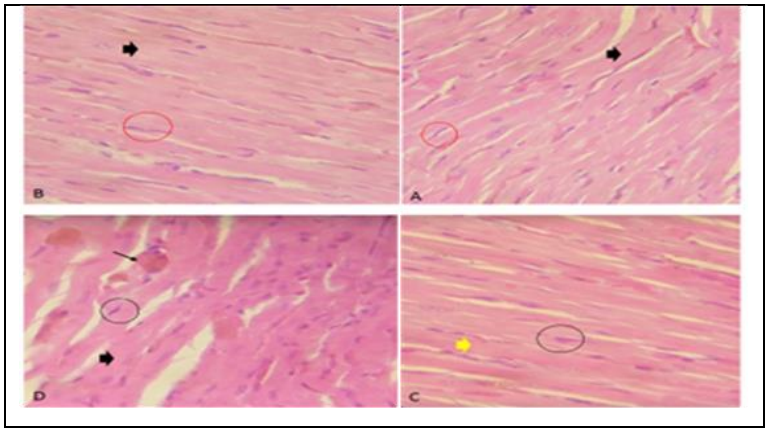

Figure 1: Photomicrograph of Coronal Section of Heart Tissues in Adult Male Sprague-Dawley Rats. Magnification: H/E x 400

a. The control group had well-organized cardiac fibers, with intercalated disc and centrally placed nucleus, without any disorientation.
b. The group treated with 500mg/kg MSG had centrally placed nucleus with slight constriction of extracellular spaces and cardiac muscles.
c. The group treated with 2000mg/kg MSG had thickened cardiac fibers, constricted extracellular spaces, and pyknotic centrally placed nucleus.
d. The group treated with 4000mg/kg MSG had severe distortion and thickness of the cardiac fibers, dilated and increased extracellular space, plaque deposition, and reduced pyknotic centrally placed nucleus.

CONCLUSION

The investigation findings suggest that monosodium glutamate administration at different doses reduces lactate dehydrogenase activity in heart tissues and lowers creatine kinase and troponin activity, while also causing changes in blood electrolyte levels. Histomorphology analysis of the heart indicates that monosodium glutamate induces distortion and dilation of heart tissues, similar to pathological conditions. Additionally, monosodium glutamate decreases antioxidant enzyme levels and increases lipid peroxidation in the heart. In summary, administering monosodium glutamate at doses of 500mg/kg, 2000mg/kg, and 4000mg/kg is toxic to blood electrolytes and heart tissues in Adult Male Sprague-Dawley rats. Therefore, moderation is important when using

monosodium glutamate to avoid health hazards caused by oxidative stress.

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