The adverse effect of long term intake of Monosodium Glutamate on kidney performance

Amer M. Hussin1*, Ali A. Tala'a2, Safa Abdul Naser Fadhil1 and Hamzah Abdulrahman Salman1

1 Medical Laboratory Techniques, College of Medical Sciences Techniques, The University of Mashreq, Baghdad, Iraq.
2 College of Veterinary Medicine, Al-Fallujah University, Iraq

*Corresponding Email: amer17173@gmail.com; amer.muttib@uom.edu.iq

Abstract. Monosodium glutamate (MSG) is a food additive that is considered as a water and environmental pollutant and affects the tissues of the living being. This study was aimed to find the effect of long-term administration of MSG on the mass of mesangial cells of the kidneys. Forty adult male rats were divided into four groups (10 each). Control groups 1&2 were supplied orally with distilled water for 30 and 60 days, respectively. Treatment groups 1&2 were supplied orally with 15 mg/kg Bwt of MSG for 30 & 60 days, respectively. Control and treatment groups were sacrificed, specimens of kidneys were obtained, fixed with 10% neutral buffered formalin, processed by Routine histological techniques, stained by Hematoxylin and eosin, and PAS (Periodic Acid-Schiff) stains then examined under the light microscope. The result found enlargement in a mesangial mass represented by hypertrophy and hyperplasia of mesangial cells leading to mesangial proliferative glomerulonephritis. Accordingly, the study showed an increase in creatinine values, indicating a disturbance in renal function. This will lead to a decrease in the sizes of the glomeruli of renal corpuscles and a relative increase of Bowman's space. With the time of the experiment, the glomerular capillaries and gates of basement membranes will be closed, resulting in renal filtration disorders. It was concluded that the long-term intake of MSG leads to indirect narrowing of the glomerular capillary lumen, causing kidney failure.

Keywords: Monosodium glutamate, Mesangium, Kidney failure, MSG

Track Name: Human, Social, Economic and Environmental Sustainability

1. Introduction

Monosodium glutamate (MSG) is also known as a vetsin powder. It is used as a flavor enhancer in food preparation. Many studies have been referred to the effects of high dosages of MSG [1, 2]. The toxicity of MSG wastewater on the growth ability of Chinese cabbage and wheat seeds was also observed. Dong et al. [3] showed MSG manufacturing in China released
ammonia into the atmosphere and maybe a potent pollutant agent. This human-made excess ammonia can cause respiratory health problems [3]. Dixit et al. reported that albino rats given 4 mg/g of body weight MSG orally for seven days showed a significant alteration in renal glomeruli with increasing the length and size of the Bowman's capsule with the widening of Bowman's space [4]. Mesangial cells are smooth muscle-like cells between the glomerular capillaries, close to the capillary lumen. Their shapes were flattened, irregular with cylindrical cell bodies and processes containing actin and myosin, giving them contractile properties. Mesangial cells act cooperatively with podocytes.

The population of mesangial cells forms about 30-40% of the total number of glomerulus cells [5]. The primary function of the mesangial cell is phagocytosis by removing the precipitates attached to the basement membrane and keeping the filtration barrier-free from debris. The mesangial cell has a contractile property in alternating the glomerulus filtration pressure [6, 7]. The anchoring filaments of mesangial cells attached to the glomerular basement membrane can decrease the flow of capillaries by altering the surface area of glomerular ultrafiltration. The functional unit of glomeruli is mesangium, podocytes, and glomerular endothelial cells through interactions of molecular signaling pathways, which are fundamental for glomerular tuft formation [8]. Mesangial cells assist the filtration by constituting part of the tuft structure of the glomerular capillary that aid in the filtration of fluids to produce urine [9].

The expansion of mesangium occurs due to an increase in extracellular matrix protein deposition [10]. The activation of metabolic pathways is a result of increased glucose levels leading to increased oxidative stress. This will finally lead to the glomerular basement membrane thickening, expansion of mesangial matrix, then fibrosis and glomerulosclerosis [11]. A previous report recommended a detailed examination to be carried out to evaluate the effects of MSG on the atmosphere, work environment, and health activities of the manufacturer's workers [12]. Furthermore, Niaz et al. reported the toxicity of MSG into community health. The results showed MSG poses harmful effects on neuron cells as well as the reproductive system [13]. In context to the above, this study aimed to focus light on the side effects of the appetizer MSG on the renal infiltration barrier.

2. Materials and methods

2.1. Experimental setup
Forty adult healthy male rats were collected from local markets in 2020; rats were divided into four groups (each 10). The control groups C1&C2 were supplied orally with distilled water for 30 and 60 days, respectively. Treatment groups G1&G2 were given orally with 15 mg/kg B.wt of MSG for 30 & 60 days, respectively. All rats were sacrificed, and the specimens were fixed in 10% neutral buffered formalin and prepared by Routine histological techniques. Slides were stained by Hematoxylin and eosin, and PAS then examined under the light microscope. Optica view seven image analysis software was used for measurements.

2.2. Statistical analysis
All data were analyzed statistically by using ANOVA one-way SPSS program version 20.

3. Results
The current results declared that the long-term intake of MSG was affected the infiltration barrier of the nephrons. The study correspondingly found a relative increase in the thickness of basement membranes, Bowman's capsule diameter, and Bowman's spaces. The study revealed hypertrophy and hyperplasia of the intraglomerular mesangial cells (Table 1). Congestion of glomerular capillaries and thickening of basement membrane was also observed in treatment groups (Figs.2-7). The values of creatinine were increased with the time of the experiment (Table 2).
Table 1. Measurement of renal corpuscles constituents in control and MSG treated groups. Different letters (A, B) denote significant (p<0.05) differences between groups

| Groups | The thickness of Bowman’s capsule basement membrane (µm) Mean± SE | Bowman’s capsule diameter (µm) Mean± SE | Bowman’s space (µm) Mean± SE | Number of mesangial cells per glomeruli Mean± SE |
|--------|--------------------------------------------------|--------------------------------------|-------------------------------|-------------------------------------|
| C1     | 0.78±0.002 B                                     | 113.9±0.15 B                         | 24.2±0.24 B                  | 10.85±2.43 B                      |
| G1     | 0.91±0.005 A                                     | 114.0±0.21 B                         | 24.5±0.12 B                  | 13.11±0.4 AB                      |
| C2     | 0.8±0.003B                                       | 113.8±0.17 B                         | 24.3±0.21B                   | 10.75±2.1B                       |
| G2     | 0.97±0.003 A                                     | 128.7±0.14 A                         | 32.8±0.07 A                  | 17.3±1.1 A                       |

Table 2. Serum creatinine (mg/dl) levels in control and MSG treated groups. Different letters (A, B, C) denote significant (p<0.05) differences between groups

| Groups | Creatinine (mg/dl) Mean± SE |
|--------|----------------------------|
| C1     | 0.63±0.003 C               |
| G1     | 1.2±0.06 B                 |
| C2     | 0.59±0.002 C               |
| G2     | 1.89±0.09 A                |
**Figure 1.** Histological section of kidney in control group after 30 days showing normal architecture. Star refers to normal Bowman's space. H and E stain (400X).

**Figure 2.** Histological section of kidney for MSG treated group after 30 days showing an increase in Bowman's space (star). H and E stain (400X).
Figure 3. Histological section of kidney for MSG treated group after 60 days showing the high increase in Bowman's space (star). H and E stain (400X).

Figure 4. Histological section of kidney for MSG treated group after 30 days showing congestion of glomerular blood vessels (blue arrows) and beginning of the process of mesangial cells proliferation (black arrow) slightly. H&E stain 400X.
Figure 5. Histological section of kidney for MSG treated group after 60 days showing mitosis in mesangial cells (black arrow) and congested capillaries (blue arrows). H&E stain 400X.

Figure 6. Histological section of kidney for MSG treated group after 60 days showing enlargement of mesangial cells (black arrows) with more apparent basement membrane (blue arrow). PAS stain. 1000X.
Figure 7. Histological section of kidney for MSG treated group after 60 days showing enlargement of mesangium and proliferation of mesangial cells (arrow) ) PAS stain 400X.

Figure 8. Histological section of kidney for MSG treated group after 60 days showing congestion and hemorrhage of blood vessels (arrows). H&E stain. 400X.
4. Discussion

The herein study stated that the renal tissue deals with MSG as a foreign body (Figure 1-8). The size of Intraglomerular mesangial cells was increased due to phagocytosis of the MSG. The mesangial enlargement sheds an external pressure on the glomerular capillaries and, in turn, on the gates of infiltration barriers of the nephrons. This was nearly similar to the findings reported earlier that the expansion of mesangium occurs due to increased extracellular matrix protein deposition [8]. The present study is consistent with the previously reported data that kidney damage may occur due to the oxidation with MSG help [14]. The increase in the thickness of the basement membrane is caused by the widening of its gates in order to get rid of this foreign body.

Table 1 showed a significant increase in the size of the basement membrane and the mesangium after 30 and 60 days, while there was a significant increase in the other constituents only after 60 days. This was because the previous components of the infiltration barrier were firstly faced the MSG present in the blood, then others come later. Despite the increase in the size and number of the intraglomerular mesangial cells (Table 1), the size of the glomeruli remains intact. Correspondingly the Bowman's space showed a relative widening that indicates the increase in the glomerular filtration rate. The mesangial cells have contractile and phagocytic characters as they are attached to the glomerular capillaries themselves. This was in agreement with the finding of [6], who mentioned that the mesangial anchoring filaments attached to the glomerular basement membrane could change the capillary flow by altering the surface area of the glomerular ultrafiltration. The current study hypothesized that this might be attributed to shifting the proliferated and enlarged mesangial cells toward the capillaries that are attached to and not toward the exterior. This will induce pressure on the glomerular capillaries leading to narrowing their lumen.

With the time of the experiment, the glomerular infiltration will be affected and finally may cease leading to kidney failure. The present hypothesis was in variance with that of [15], who reported that the decrease in the size of glomeruli was attributed to sclerosis and fibrosis of the interstitial tissue of the glomeruli. As we regarded the endothelial cells and podocytes as part of the infiltration barrier, they lose the capability to divide. It was concluded that the mitotic figure seen in the glomeruli belonged only to the mesangial cells. This is confirmed with the result of [16], who stated that the normal podocytes of humans are quiescent cells and differentiated terminally. It is not understood why the failure of podocyte proliferation in response to most injury forms. Increasing values of serum creatinine in this study indicate that we are going toward kidney disorders.

5. Conclusion

It was concluded that the long-term intake of MSG causes enlargement of the mesangium. This will adversely affect the glomerular infiltration of the kidney through pressing on their intraglomerular capillaries and narrowing their lumen. We strongly suggest further investigation be carried out to understand the effects of MSG on humans.

References

[1] Albrahim T and Binobead M A 2018 Roles of Moringa oleifera Leaf Extract in Improving the Impact of High Dietary Intake of Monosodium Glutamate-Induced Liver Toxicity, Oxidative Stress, Genotoxicity, DNA Damage, and PCNA Alterations in Male Rats Oxidative medicine and cellular longevity 2018 4501097
[2] Jubadi F F, Mathalagan R D, Noor M M, Taib I S and Budin S B 2019 Monosodium glutamate daily oral supplementation: study of its effects on male reproductive system on rat model Systems biology in reproductive medicine 65 194-204
[3] Dong L, Li Y, Wang P, Feng Z and Ding N 2018 Cleaner production of monosodium glutamate in China Journal of Cleaner Production 190 452-61
[4] Dixit S G, Rani P, Anand A, Khatri K, Chauhan R and Bharihoke V 2014 To study the effect of monosodium glutamate on histomorphometry of cortex of kidney in adult albino rats Renal failure 36 266-70
[5] Alpers C E and Hudkins K L 2018 Pathology identifies glomerular treatment targets in diabetic nephropathy Kidney Res Clin Pract 37 106-11
[6] Ryan D, Sutherland M R, Flores T J, Kent A L, Dahlstrom J E, Puelles V G, Bertram J F, McMahon A P, Little M H, Moore L and Black M J 2018 Development of the Human Fetal Kidney from Mid to Late Gestation in Male and Female Infants EBioMedicine 27 275-83
[7] Takano K, Kawasaki Y, Imaizumi T, Matsuura H, Nozawa R, Tannji M, Suyama K, Isome M, Suzuki H and Hosoya M 2007 Development of glomerular endothelial cells, podocytes and mesangial cells in the human fetus and infant The Tohoku journal of experimental medicine 212 81-90

[8] Schlöndorff D and Banas B 2009 The mesangial cell revisited: no cell is an island Journal of the American Society of Nephrology : JASN 20 1179-87

[9] Marciano D K 2019 Mesangial Cells: The Tuft Guys of Glomerular Development Journal of the American Society of Nephrology : JASN 30 1551-3

[10] Muraoka H, Hasegawa K, Sakamaki Y, Minakuchi H, Kawaguchi T, Yasuda I, Kanda T, Tokuyama H, Wakino S and Itoh H 2019 Role of Nampt-Sirt6 Axis in Renal Proximal Tubules in Extracellular Matrix Deposition in Diabetic Nephropathy Cell Reports 27 199-212.e5

[11] Zhang J, Wang Y, Li L, Zhang R, Guo R, Li H, Han Q, Teng G and Liu F 2018 Diabetic retinopathy may predict the renal outcomes of patients with diabetic nephropathy Renal failure 40 243-51

[12] Rim K-T 2017 Toxicological evaluation of MSG for the manufacturing workers' health: A literature review Toxicology and Environmental Health Sciences 9 1-11

[13] Niaz K, Zaplatic E and Spoor J 2018 Extensive use of monosodium glutamate: A threat to public health? EXCLI J 17 273-8

[14] Sharma A 2015 Monosodium glutamate-induced oxidative kidney damage and possible mechanisms: a mini-review Journal of Biomedical Science 22 93

[15] Alsaad K O and Herzenberg A M 2007 Distinguishing diabetic nephropathy from other causes of glomerulosclerosis: an update Journal of clinical pathology 60 18-26

[16] Shankland S J, Eitner F, Hudkins K L, Goodpaster T, D'Agati V and Alpers C E 2000 Differential expression of cyclin-dependent kinase inhibitors in human glomerular disease: role in podocyte proliferation and maturation kidney international 58 674-83