Effects of Monosodium Glutamate and Acrylamide on The Liver Tissue of Adult Wistar Rats

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Abstract: The present work aimed to elucidate any histological changes in liver tissue of rats when treated with the commonly used food additive; Monosodium glutamate (MSG) and Acrylamide (ACR) ;which is the basic unit in polyacrylamide production and used in water treatment. Tha samples of this study was forty adult male wistar rats. They were divided into four equal groups. Group I was the control group, A single oral daily dose of 30mg/ kg/ day of (MSG) and of (ACR) for continuous 4 weeks was administered to Group II (MSG treated) and Group III (ACR treated) respectively. Group IIII received a single oral daily dose of both substance (MSG & ACR). The histological study of liver sections of Group II showed vacuolar degeneration of hepatocytes cords, nuclei pyknosis and congestion of blood vessels. The liver treated with (ACR) appeared hepatocytes necrosis, disruption of blood sinusoid, and decreased number of kupffer cells. However, similar histological change reported in group II and III were noticed in Group IIII with addition to some hepatocytes lysis and blood vessels fibrosis. According to findings in the experimental animal (male rats liver), we can conclude that the MSG & ACR cause hepatoxicity and tissue alteration .

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***Key words*:** Monosodium glutamate, Acrylamide, Rat, Liver, Histopathology.

1. Introduction

Monosodium glutamate (MSG) is commonly consumed as a flavor enhancer or food additive (Moore, 2003; Alao et al, 2010). MSG is the sodium salt of the non-essential amino acid-glutamic acid (NHIC, 2008). MSG contains 78% of glutamic acid, 22% of sodium and water (Samuels, 1999).It is known to have some adverse effects in humans and experimental animals. It is metabolized in liver and eliminated through the kidney (Schwerine et al, 1950). Glutamic acid is transformed into alanine in intestinal mucosa and lactate in liver (Bhattacharya et al., 2011). Chronic administration of MSG (4mg/k and above) induced oxidative stress in experimental animals.MSG causes retinal degeneration, endocrine disorder, addiction, stroke, epilepsy, brain trauma, neuropathic pain, schizophrenia, anxiety, depression, Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis (Adrienne, 1999; Eweka and Adjene, 2007). Subsequently it was documented that MSG produces oxygen derived free radicals (Singh and Ahluwalia, 2003). It is reported that MSG causes changes in the liver parenchyma of mice around central vein, dilated sinusoids, inflammatory cells and nuclei were pyknotic (Bhattacharya et al, 2011).

Acrylamide (ACR) is an alpha, beta-unsaturated vinyl monomer of poly-acrylamide (EL-Bohe et al, 2011), products used in water purification, grouts, packaging, and scientific research. Acrylamide was formed in food as a result of a heat-induced reaction between two naturally occurring ingredients; the amino acid asparagine and reducing sugars (Mottram et al., 2002; Stadler et al., 2002). Acrylamide is one of the most important contaminant in the environment, which was shown to be a neurotoxicant produces peripheral neuropathy in animals (Hashimoto and Aldridge, 1970). It is reproductive toxicant and carcinogen in animals (El-Assouli, 2009). However, Butterworth, et al., (1992) reported that ACR induces dominant lethal mutations in male rat germ cells and tumors in a variety of organs, including the scrotum, thyroid and mammary glands. Histopathological investigation revealed necrotic and degenerative changes in the liver of acrylamide treated rats (EL-Bohe et al, 2011). ACR-induced hepatotoxicity as the metabolism of ACR mediated through glutathione conjugation in the liver tissue (Miller et al, 2004). So, most MSG and ACR are sold in open markets and stores in Saudi Arabia. Not many workers have observed detailed histological features as effect of MSG and ACR in liver tissue. Therefore, with the objective to know if a doses of 30mg/kg MSG or ACR are toxic on liver tissue when administered to male rats.

2.Material and Methods

2.1.Materials:

2.1.1.Compounds under investigation:

- Monosodium glutamate (MSG) purity (99%) was sold in most open market in Jeddah of Saud Arabia under the license of Ajinomoto co.INC. Tokyo, Japan.

- Acrylamide (ACR) purity (99.9%) was supplied from Sigma chemical company. The applied doses of both substances were selected according to Tyl and Friedman (2003).

2.1.2. Experimental Animals

Experiment was conducted on (40) adult male wistar rats of 8-10 weeks old. Average weight of 220±7.88g. According to OECD (2010a,b) guide line on the design and conduct of chronic toxicity, and the council of Europe, (2006) recommendations on rodents housing. Animals were obtained from the animal house of the King Saud Center for Medical Research, King Saud University in Riyadh. Were breeding animals within the room well ventilated range temperature between 22-25 º C and an appropriate lighting ,humidity and feediing dry balanced meals provided by the General Organization for Grain Silos and Flour Mills in Jeddah, with a constant source of water.

2.2.Methods:

2.2.1.Experiment design

- The animals were divided into 4 groups:

***Group1:**contained 10 mice which received daily 0.2 ml single interaperitoneal (I.P) injection of saline solution.

***Group2:** contained 10 mice which received daily a single dose of 30mg /kg I.P injection of Monosodium glutamate dissolved in 0.2 ml of saline solution.

***Group 3:** contained 10 mice which received daily a single dose of 30mg /kg I.P. injection of Acrylamide dissolved in 0.2 ml of saline solution.

* **Group4:** contained 10 mice which received daily a single dose of 30mg /kg I.P. injection of Acrylamide and Monosodium glutamate respectively as the same manner

- Several parameters were recorded:

1-The behavioral and morphological changes that have taken place

2-The body weight of the rats weekly; at the beginning to end of the experimental periods.

3- Changes in the internal organs .Rats were dissected 24 hours after the end of experimental period 4 weeks.

- Liver samples were collected, cut into small pieces and then put in 10% neutral buffered formalin, embedded in paraffin. Sections of 1-3 µ were stained with haematoxylin and eosin for histological examination (Bancroft and Gamble., 2002; Hummdi, 2012).

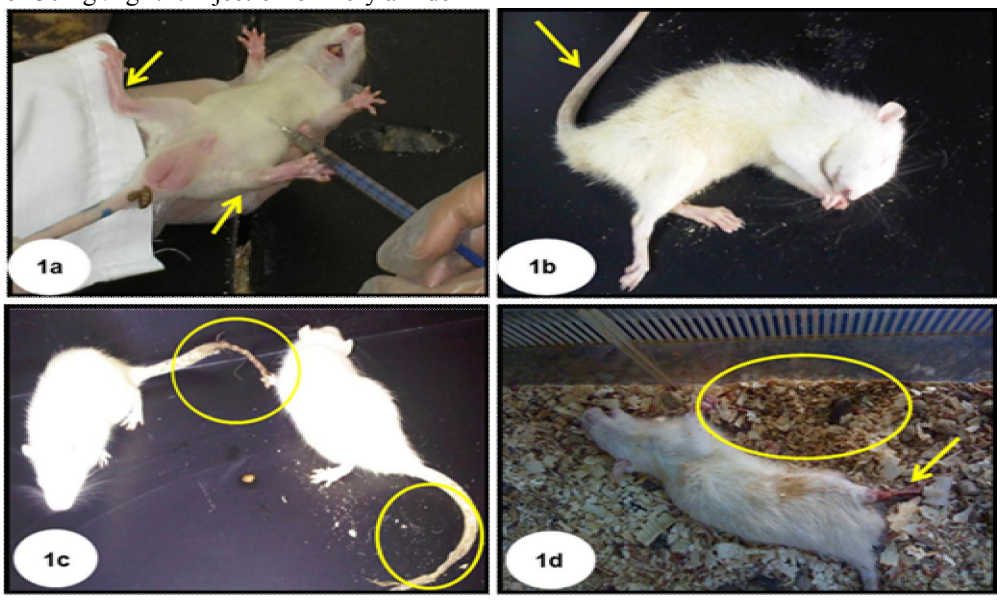
***2.2.2.*Statistical analysis**

The results were analyzed using the Statistical Package of Social Science (SPSS) version 18 software**.** Comparisons between experimental groups were made using the student's t- test at $P \leq 0.05$ level of significance.

3.Results

3.1. Behavioral and morphological observations

Severe diarrhea, frequent urination with a repulsive smell, increased appetite and weak limb movement were observed in the rats group treated with MSG (GII) comparing to control rats.Whereas, the rats in group given ACR (GIII) display anorexia, weakness, fading, paralysis limb movement, lack of resistance and severe ulceration of the tail **(Figs.1a-c).** However, rats in group (GIIII) which treated with MSG and ACR suffered from the same symptoms indicated in groups GII and GIII **(Fig.1a,d).**



(Figs. 1a-d):(a,b)*control wistar rat showing normal hind limbs and tail(arrows).* ***(c)*** *ACR treated rats showing tail ulceration.****(d)*** *MSG and ACR treated rat showing diarrhea, frequent urination and hind limb paralysis.*

3.2. Body weight

There were a highly significant changes between mean values of body weight gain in experimental groups compared to control group **(Fig. 2), (Table 1).**

A significant increase in the rats' body weight was observed in group GII administrated MSG. ACR administration induced highly significant decreased in body weight of rats in group GIII. No significant increased were observed in body weight in rats of group GIIII taken both MSG and ACR.

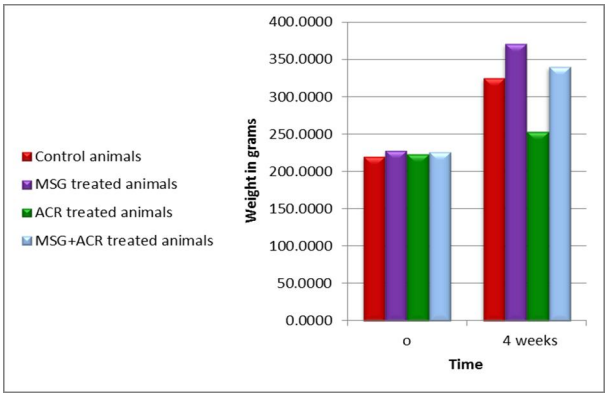


Figure 2: Effect of MSG and ACR on the total body weight of rat

Table 1: Mean and deviation of body weight for control and treated rats at end of experimental period.

Groups / Time	Control animals	MSG treated animals	ACR treated animals	MSG+ ACR treated animals
0 day Mean ±S.D P	220.0000±7.88106	228.0000±5.02563 P=0.219	223.0000±7.71068 P=0.777	226.0000±7.05698 P=0.196
4 weeks Mean ±S.D P	325.0000±6.82330	371.0000±4.67486 P=0.038*	253.3000±4.88888 P=0.003*	340.0000±2.09401 P=0.131

P> 0.05 not Significant, *P < 0.05 Significant ; or ** p < 0.01 high Significant S.E : Standard Error of Mean

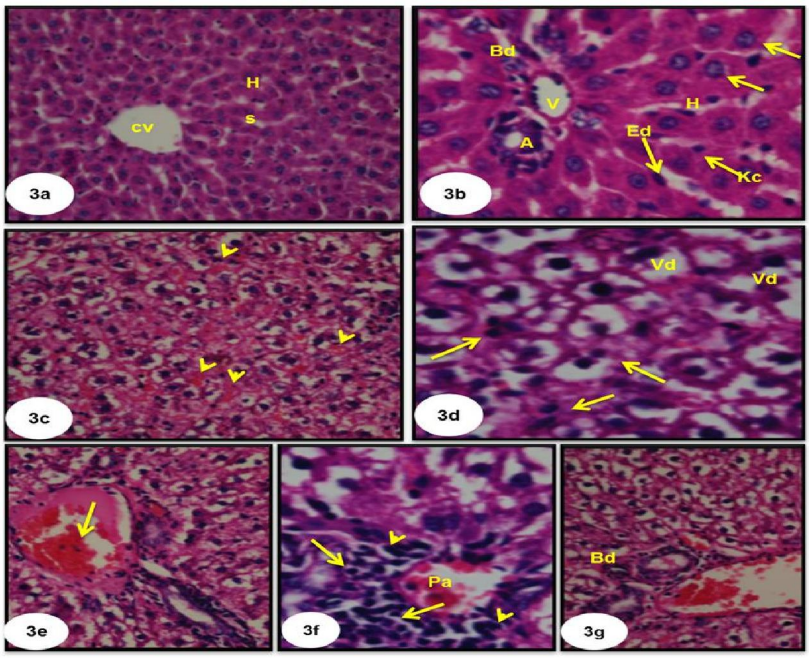
3.3.Histological Results:

Control sections of liver revealed normal histological features with hepatic lobules. each of which consists of cords of regularly arranged hepatocytes enclosing the sinusoidal network and central vein that located in the center of the lobule. The hepatocytes are polygonal in shape and have clear round to slightly oval nuclei, one or two nucleoli. The blood sinusoids lining with non-parenchymal cells include Kupffer cells and endothelial cells. The portal area contained branches from hepatic artery, portal vein and bile duct (Figs.3a,b).

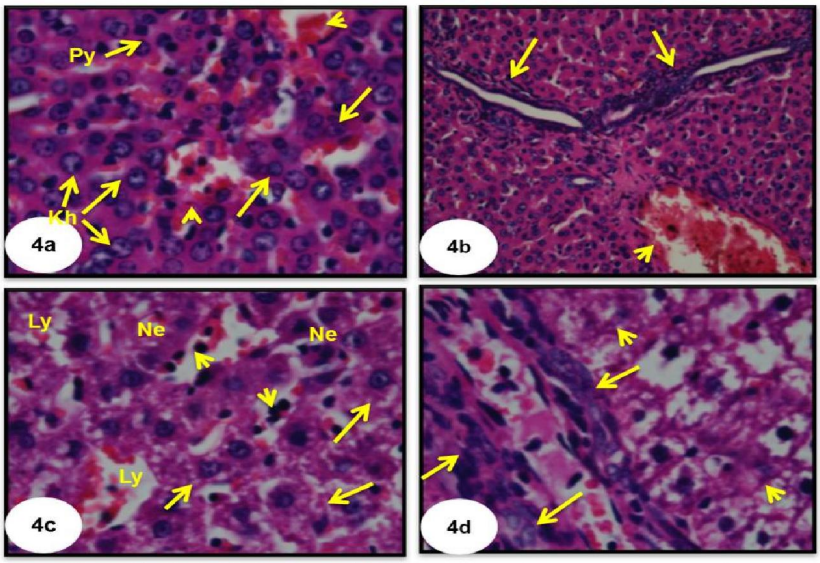
However, animals treated with MSG centrolobular hepatocytes zones revealed sever vacuolar cytoplasmic degeneration with nuclei pyknosis and polymorphism, accompanied by blood sinusoids congestion and odematous of liver parenchyma (Figs.3c,d) . Congestion of portal veins with red blood cells stasis(Fig.3e) and massive cellular exudate of lymphocytes and macrophages around portal areas (Fig.3f). Bile ducts proliferation also been showed (Fig.3g).

On the other hand, the liver tissues of animals treated with ACR showed diffuse centrolobular hepatocytes degeneration and necrosis, disruption of blood sinusoids with decreased of kupffer cells number and interstitial heamorahges (Fig.4a). The nuclei appeared pyknotic and some showed signs of fragmentation (Karyrrhexis) and disintegration (Karyolysis) (Fig.4a). Elongated of bile ducts and congestion of blood vessels in portal areas can be seen (Fig.4b).

In livers tissue treated with MSG & ACR displayed hepatocytes vacuolation and necrosis which led to tissue lysis with cellular aggregates, dilation of blood sinusoids and kupffer cells pyknotic **(Fig.4c).** In addition to, fibrosis of blood vessels in portal area which surrounded by necrotic cells **(Fig.4d).**



(Figs.3a-g):((a,b) Light microscope images of control sections of liver tissue showing cords of hepatocytes (H) with round nuclei(arrows) and nucleoli, central veins(Cv), blood sinusoids(S), Kupffer cells (Kc), endothelial cells(Ed) and portal area note; Bile duct (Bd), Artery (A) and vein(V) 400x,1000x,H&E. **(c-g):** Sections of rat liver tissues treated with MSG.**(c,d):** vacuolar cytoplasmic degeneration(Vd) of hepatocytes and nuclei pyknosis, blood sinusoids congestion (head arrows) and odematous with inflammatory exudates(arrows), 400x, 1000x, H&E. **(e)** congestion of portal vein with erythrocytes stasis(arrow), 400X, H&E.**(f)** cellular exudate of lymphocytes (arrows) and macrophages(head arrows) around portal area(Pa), 1000X,H&E.**(g)** bile duct proliferation(Bd), 400X,H&E.



(Figs.4a-d): {a,b}Sections of ACR treated rats liver: **(a)** hepatocytes degeneration and necrosis(arrows), blood sinusoids disrupted with interstitial hemorrhages(head arrows), pyknotic (Py) and Karyrrhexis(kh),1000x,H&E.**(b)** bile ducts elongated (arrows) and congestion of blood vessel (head arrow) in portal area,400x,H&E. **(c,d)** Sections of rats liver tissues treated with MSG and ACR: **(c)** hepatocytes vacuolation (arrows), necrotic($_{Ne}$) and lysis (Ly) with cellular infiltration (head arrows),1000x, H&E.**(d)** fibrosis of portal area vein (arrows) surrounded by necrotic cells(head arrows), 1000x,H&E.

4. Discussion

Abnormal neurobehavioral changes recorded in the present work in animals treated with MSG, coincide with (Bhattacharya et al., 2011) who showed less limb movement. Whereas, affect locomotion, and sexual behavior were observed by (Alao *et al*., 2010) in male and female rats. So, administration of ACR to male rats resulting in marked behavioral and morphological manifestations in present study may attributed to ACR neurotoxicity that causing hind limb dysfunction which lead to inability to get food, In addition, ACR may cause alterations in thirst and hunger regulation centers in hypothalamus (WHO, 1985). EL-Bohe et al,(2011) added ataxia, increased landing of the limbs, weakness of the muscles, general emaciation in rats given ACR. (Shukla et al., 2002) found that exposure of rats to ACR caused hind limb paralysis in 58% of the animals, they attribute these findings to ACR neurotoxicity.

On the other hand, observations of the recent study indicated significant increase in body weight gain of rats MSG treated group. Similar observations were also recorded by others in mice, Bhattacharya et al 2011, in rats (Onyema *et al* (2006;Inuwa *et al*, 2011) and in female rats (Tawfik and Al Bader,2012). MSG given could induce an increase in energy intake (Bergen et al., 1998) which could lead to obesity (Mozes et al., 2004) or alter the metabolism levels of carbohydrates, lipids and proteins in rats (Diniz et al, 2004). However, (Onyema et al., 2006; Park et al, 2000) attributed the increased body weight to inflammation and edematous of liver tissue. In contrast, treated rats in this work with ACR showed decrease in body weight gain. These findings are similar to those confirmed by EL-Bohe et al, (2011) in rats and (Hogervors et al, 2007) in human. The steady weight gain in groups treated with MSG and ACR possibly due to organs failure and shrinkage in subsequent toxicity by compounds investigated (Hamaoka and Kusunoki, 1986).

Examination of control liver sections of male rats pronounced large extent of corresponds with liver structure previously mentioned in rodents and in other mammals (Moody and Hammock, 1987; Junqueira and carneiro, 2005; Hummdi.and Habashi, 2010**).**

The most marked signs of liver tissue impairment and vacuolations in the present study were observed in centrolobular hepatocytes zones than portal zones hepatocytes in all treated groups. These results agree with (Bhattacharya et al 2011) work, were it was noted the vacuolations of hepatocytes were more pronounced around the central vein in the mice injected by MSG for 75 days. In addition, ACR treatment induced vacuolations and necrosis in liver hepatocytes of chick embryos at dose of 0.1mg/kg (Kedam et al., 2012). (Cheville, 2009) reported that centrolobular hepatocytes are typically the primary site of toxic injury; they have more surface receptors for toxins and less oxygen. (Abdel Hameed, 2004) described the vacuolation of hepatocytes as ballooning degeneration and interpreted it as a kind of cellular defensive mechanism against injurious substances. (Cheville, 2009) added that these vacuoles are responsible for collecting the injurious elements and preventing them from interfering with the biological activities of these cells.

As were appeared in the present study the exposure to the MSG and ACR toxins turned the degenerative changes into necrotic damage, and tissue lysis. These observation is in consonance with Eweka and Om, Iniabohs (2007) findings on rats liver received 3mg and 6mg of MSG for two weeks, and rats given 60mg of MSG for two month with vessels fibrosis (Waer and Edress, 2006). Bopanna et al. (1999) reported histological changes on rats liver and kidney fed with monosodium contaminated food, they found that there were foci of necrosis, fatty degeneration and micro vascular alterations in liver, whereas, in kidney, patchy tubular necrosis and interstitial infiltration were present. However,(Nagao et al., 2007; Vasundhara in 2005) reported that Acrylamide treatment in the liver of rats showed frequent necrosis and bleeding. (Onyema et al .,2006; EL-Bohe et al,2011) added that administration of MSG or ACR could significantly increase the activities of the serum enzyme marker of hepatocellular injury aminotransferase (AST) ,alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (GGT) in rats. (Sanad *et al*., 1997) who suggested that the cellular destructed lysosomes to facilitate the process of autolysis which confirmed the current result.

Current work revealed pyknosis and karyolysis of cell nuclei may indicate the loss of functional efficiency of the cells. Similar results have been demonstrated by (Ortiz et al., 2006) on male rats obtained 4mg/kg of MSG. Also, this result is consistent with the findings by (Kedam et al, 2012) who indicating hypertrophy of nuclei and pycnotic nuclei in acrylamide treated chick. (Abdel Hameed 2004) stated that the nuclear damage is a sequence of cytoplasmic damage. Sinusoidal dilations, hemorrages and bile ducts proliferation also observed in acrylamide treatment rats(Nagao et al,2007; EL-Bohe et al., 2011).In agreement with these results (Schiff and Nagy , 2004) stated that the cells lining the bile ducts are stem cells that activated and prolifered with necrosis or lysis of liver cells.

The main encountered inflammatory cells in the recent work were, lymphocytes and macrophage. Lymphocytes are predominant in intoxication, viral and protozoal diseases, and macrophages signs of chronic inflammation. These findings were parallel with (Cheville, 2009) who confirmed that activation of macrophages occurs in the presence of particulate material and strong microbial antigens. Moreover, (Curran 1996; Hummdi and Habashi ,2010) reported that the macrophages destroyed the causes of damage and injured tissues, while lymphocytes produce anti-toxins and accelerate cell healing.

Conclusion

Basing on the obtained results, MSG and ACR are capable of producing alterations in the body weight and liver tissue when consumed in high doses. It is recommended that further research have to be carried out in order to investigate the effects of MSG and ACR on specific organ tissues. It is also recommended that the kinetics and mechanism of action of MSG and ACR in animals and humans be studied.

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