The Possible Ultra Structural Ameliorative Effect of Taurine in Rat's Liver Treated with Monosodium Glutamate (MSG)

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Abstract: Monosodium glutamate (MSG) is a food additive with a wide range of biological effects but its high dose and long period of using can cause a toxic effect on liver. Taurine is a derivative that produces antioxidant in many tissues including liver. The current research concerned with biochemical, histopathological and ultra structural changes in rats liver treated with MSG and throw light on the possible ameliorative effect of taurine – 150 male albino rats were divided into five group each containing 30 rats (controls, taurine, MSG, therapeutic and protective group). Serum AST, ALT, ALP and bilirubin (direct and total) were measured, as well as histopathological and ultrastructural changes in liver tissues were examined in all groups. The rats received MSG orally in a dose 400 mg/Kg. B. wt for 8 weeks (MSG group), while taurine induced orally in a daily dose at 1000 mg/Kg. B. wt alone (Taurine group) or after MSG (therapeutic) or before MSG (protective) for the same period, in addition to frank control group received orally 2 ml saline per day during the experiment. The results showed marked and gradual increase in the serum levels of AST, ALT, ALP and bilirubin (direct and total) in MSG group as compared to control group. The histopathological structure of the same group showed hepatic and local hemorrage as well as necrosis of hepatocytes with pyknotic nuclei after 4 weeks of the treatment, while after 8 weeks portal edema, thickening in wall of bile duct and portal infiltration were observed. Ultra structure examination in the same group after 8 weeks showed hyaline degeneration; rough endoplasmic reticulum with irregular nuclear membrane and cytoplasm rich in glycogen granules, Interestingly, the results showed a significant restore of hepatic injury as evidenced by attenuation of hepatocellular enzyme and bilirubin release and reduction of hepatocyte necrosis and then portal infiltration in therapeutic group reduction of hepatocyte necrosis and then portal infiltration therapeutic group. While complete normalization in plasma ALT, AST, ALK and bilirubin levels with complete restore of histological and ultra structural arrangement of hepatocyte were observed in protective group.

In conclusion, the results confirm the hepatotoxic effect of MSG and improve the hepatoprotective effect of taurine, especially when it administrated as a protective substance than therapeutic. Also, we advice to add a suitable dose of taurine to any food containing MSG as a food additive.

INTRODUCTION

Monosodium glutamate is a substance widely used as flavoring agent in the whole world. It is the sodium salts of glutamic acid and a form of glutamate. It is absorbed very quickly from gastrointestinal tract and could spike blood plasma levels of glutamate [1].

In addition, MSG causes edema-degeneration –necrosis in liver [2] and induced the oxidative stress and hepatotoxicity in rats [3]. Moreover, MSG treatment of mice induces obesity and diabetes with steatosis and steatohepatitis and they suggested that MSG should be potentially withdrawn from the food chain [4].

Taurine, one of the known amino acids has many important and beneficial effects on the human body. It has been implicated in many physiological functions, pharmacological actions and pathological conditions [5]. Other physiological roles attributed to taurine, includes membrane stabilization, antioxidation, osmoregulation, neuromodulation, detoxification and regulation of calcium homeostasis [6].

Taurine fulfills a role in promoting hepatic stellate cell's apoptosis. In the case of hepatic fibrosis; it mitigates the liver injury, decrease the expression of transforming growth factor beta-1 and relieves hepatic fibrosis [7]. In addition, it was effective in the prevention of lipopolysaccharide-induced hepatotoxicity and pro-oxidant status [8], reduces oxidative stress and prevents progression of hepatic fibrosis in CCl_4-induced hepatic damage rats as well as inhibits transformation of the hepatic stellate cells [9], protects the integrity of the hepatic tissues by stabilizing the reactive oxygen species mediated lipid peroxidation and protein carbonyl formation and it acts as antioxidant in tamoxifen-induced hepatotoxicity [10], plays a beneficial role for the prevention of cisplatin hepatotoxicity [11] and protects the liver against ethanol-induced oxidative injury *via* its effects on the sulfur-amino acid metabolism [12].

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The target of the present investigation is concerned with the possible biochemical, pathological and Ultra structural (E/M) changes that may occur in rats' liver under the effect of MSG (food additive) and shed light on the possible protective and therapeutic effects of taurine.

MATERIALS AND METHODS

Materials

One hundred and fifty male albino rats (rattus) were used in the present studies. The weights of rats ranged from 120-130grams and their ages ranged from 2-3 months and obtained from the Egyptian Organization for Biological product and Vaccines.

Animals were maintained on a standard pellet diet and water, for 7 days, the diet consists of about 20% protein, 5% fibers, 3.5% fats and 6.5% ash and supplied with vitamins mixtures. Feed and water were available at the time of experimental period. The animals were housed in suitable cages (each cage contain 10 rats) and kept at optimal conditions of temperature and humidity.

Chemicals

The chemical used monosodium glutamate (MSG) from Fluca Co. with purity >98% NT and taurine supplied by Sigma with a 99% purity. Both drugs were orally administered.

Experimental Animal Grouping

The animals were divided into 5 equal groups each contain 30 male rats:

1-Control Group

Animals of this group received orally saline daily, parallel to the drug treated groups.

2-Monosodium Glutamate (MSG) Treated Group

The rats received a daily dose of MSG (400mg.kgB.wt./ d.) for eight weeks.

3-Taurine Treated Group

The rats received orally a daily dose of taurine (1000mg. kgB.wt./d.) for eight weeks.

4-Therapeutic Group

Animals of this group received oral dose of MSG (400mg.kgB.wt./d.) then treated orally after one hour with taurine in a dose of (1000mg.kgB.wt./d.) for eight weeks.

5-Protected Group

Animals of this group received oral dose of taurine in a dose of (1000mg.kgB.wt./d.) then after one hour they administered with oral dose of MSG (400mg.kgB.wt./d.) for eight weeks.

Blood Samples

Blood sampling was made after 2, 4, 6and 8 weeks. Samples were drawn, after overnight fasting (using a special micropipettes introduced through the inner contnuse of rats orbit into the cavernus sins and the head of the rat was tilted down) in clean, and sterile serum tubes. Blood samples were centrifuged for 10 minutes, at 3000 r. p. m. within an hour of the blood collection and the sera were obtained to measure the liver functions:

Serum aspartate-amino transferase (AST) and alanine-amino transferase (ALT) were determined calorimetrically [13], using commercial kits purchased from the Biomerieux, France.

Serum alkaline phosphatase activity (ALP) activity was determined calorimetrically [14], using commercial kits purchased from the Biomerieux, France.

Serum bilirubin (Direct and Total) was measured [15]. The reagents used were kits purchased from the Boehringer, Germany.

Histopathological Studies

After scarification and dissection, liver was removed immediately and fixed in 10%formal saline and neutral buffered formalin for 7 days, then the tissue was washed and dehydrated in ascending grads of ethyl alcohol cleared in benzene and impregnated in paraffin for 1. 5 hour in the oven at 55°C. Serial section 5µm was cut and stained with Hematoxylin and Eosin (H&E) as described by [16].

Electron Microscopic Study

The liver from all groups were examined by E. M.

RESULTS

Biochemical, histopathological and electron microscopic examination were done for liver to evaluate the possible therapeutic and protective effect of taurine against the hepatotoxic effect of MSG.

The Table **1** showed that all liver enzymes measured in this work (AST, ALT, ALP) and bilirubin (Direct and Total) were non significantly changed ($P>0.05$) from control in taurine treated group, while in MSG group the latter enzymes and bilirubin (D and T) were significant, ($P< 0.01$) elevated after 2, 4, 6 and 8 weeks, but these elevations were markedly decreased, especially in protective than in therapeutic group after 8 weeks.

Supporting, in MSG group, Fig. (**2** and **3**) showed cellular and nuclear pleomorphism and apparent vacuolation in the cytoplasm of the hepatocytes. Areas of necrosis and hemorrhage involved most of the hepatic parenchyma were noticed. The hepatocytes in numerous hepatic lobules showed variation in nuclear size, some have small nuclei, while in others the cells were large with longer nuclei. The blood vessels are congested with an increase in Kupffer cells. At the peripheral zones of the hepatic lobules the hepatocytes were markedly vacuolated.

In Fig. (**4a**), liver of rat in therapeutic group showed, extensive diffuse fatty degeneration, and Fig. (**4b**), in protective group, showed mild congestion and absence of necrosis with limited fatty change of the hepatocytes.

Table 1. The Level of ALT, AST, ALP, and Bilirubin (Direct & Total) in the Different Experimental Groups at the Different Periods of the Study (Liver Function)

Experimental Groups	Parameters	Periods of Study (Weeks)				F-ratio
		2 weeks	4 weeks	6 weeks	8 weeks	
Control	ALT (U/L)	10.2 ± 0.24 a	10.1 ± 0.23 a	10.3 ± 0.21 a	10.4 ± 0.26 a	0.286 NS
	AST (U/L)	11.2 ± 0.24 a	11.0 ± 0.25 a	11.3 ± 0.21 a	11.4 ± 0.26 a	0.332 NS
	ALP (U/L)	112 ± 7.13 a	113.2 ± 7.2 a	117.9 ± 7.3 a	123.6 ± 7.2 b	0.53 NS
	D.bilirub. (mg/dl)	0.185 ± 0.014	0.175 ± 0.014	0.192 ± 0.013	0.196 ± 0.015	0.412 NS
	T.bilirub. (mg/dl)	0.7 ± 0.05 b	0.67 ± 0.05 b	0.69 ± 0.03 b	0.76 ± 0.06 b	0.586 NS
TAURINE (1000mg/kg/d)	ALT (U/L)	9.1 ± 0.45 a	8.6 ± 0.45 a	8.9 ± 0.50 a	9.9 ± 0.34 a	1.56 NS
	AST (U/L)	10..1 ± 0.45 a	9.7 ± 0.42 a	9.9 ± 0.50 a	10.9 ± 0.34 a	1.448 NS
	ALP (U/L)	107.1 ± 8.40 a	100.1 ± 8.09 a	100.8 ± 8.57 a	113.5 ± 6.7 ab	0.62 NS
	D.bilirub. (mg/dl)	0.192 ± 0.015	0.173 ± 0.016	0.175 ± 0.016	0.187 ± 0.013	0.347 NS
	T.bilirub. (mg/dl)	0.60 ± 0.04 a b	0.56 ± 0.03 ab	0.56 ± 0.04 a	0.57 ± 0.03 a	0.303 NS
MSG (400 mg.kg./d)	ALT (U/L)	12.6 ± 0.70 Ab	21.2 ± 2.04 BC	31.3 ± 1.57 Cc	50.0 ± 3.08 Dd	62.15 **
	AST (U/L)	13.6 ± 0.70 Ab	22.2 ± 2.04 BC	32.3 ± 1.57 Cc	51.0 ± 3.08 Dd	62.15 **
	ALP (U/L)	162.2 ± 3.8 Ad	197.5 ± 4.8 Bd	227.5 ± 4.8 B d	258.5 ± 6.7 Dc	64.59 **
	D.bilirub. (mg/dl)	0.564 ± 0.014	0.574 ± 0.012	0.591 ± 0.011	0.675 ± 0.01	18.24 **
	T.bilirub. (mg/dl)	1.589 ± 0.04	1.671 ± 0.03 ab	1.782 ± 0.04 a	1.801 ± 0.029 a	7.99 **
MSG (400 mg/kg/d) Then TAURINE (1000 mg/kg/d) [Therapeutic]	ALT (U/L)	14.2 ± 0.55 A c	17.2 ± 0.55 A b	22.5 ± 0.6 Bd	30.5 ± 1.96 C b	42.13 **
	AST (U/L)	15.2 ± 0.55 Ac	18.2 ± 0.55 A b	23.5 ± 0.6 Bb	31.5 ± 1.96 C b	42.13 **
	ALP (U/L)	133 ± 3.2 A b c	155 ± 4.1 BC b	148 ± 3.05 Bb	158.6 ± 3.0 C c	11.39 **
	D.bilirub. (mg/dl)	0.67 ± 0.011	0.659 ± 0.011	0.62 ± 0.011	0.60 ± 0.013	8.10 **
	T.bilirub. (mg/dl)	0.95 ± 0.03 a	0.93 ± 0.02 a	0.88 ± 0.03 a	0.80 ± 0.03 a	5.76 **
TAURINE (1000mg//kg/d) Then MSG (400 mg/kg/d) [protective]	ALT (U/L)	9.3 ± 0.36 a	9.2 ± 0.32 a	9.2 ± 0.32 a	9.6 ± 0.33 a	0.32 **
	AST (U/L)	10.3 ± 0.36 a	10.2 ± 0.32 a	10.2 ± 0.32 a	10.6 ± 0.33 a	0.31 **
	ALP (U/L)	107.2 ± 8.09 a	101.2 ± 5.96 a	101 ± 6.17 a	113.5 ± 6. 7 a b	0.76 **
	D.bilirub. (mg/dl)	0.173 ± 0.015	0.173 ± 0.015	0.167 ± 0.014	0.186 ± 0.014	0.27 **
	T.bilirub. (mg/dl)	0.58 ± 0.04 a b	0.55 ± 0.05 a b	0.56 ± 0.03 a	0.52 ± 0.03 a	0.39 **
F-ratio	ALT (U/L)	22.38 **	42.58 **	215.60 **	144.16 **	
	AST (U/L)	22.38 **	42.09 **	215.60 **	144.31 **	
	ALP (U/L)	10.652 **	35.72 **	56.09 **	102.46 **	
	D.bilirub. (mg/dl)	1.57 N S	0.57 N S	0.602 **	0.76 N S	
	T.bilirub. (mg/dl)	1.87 N S	1.46 N S	1.71 N S	3.94 **	

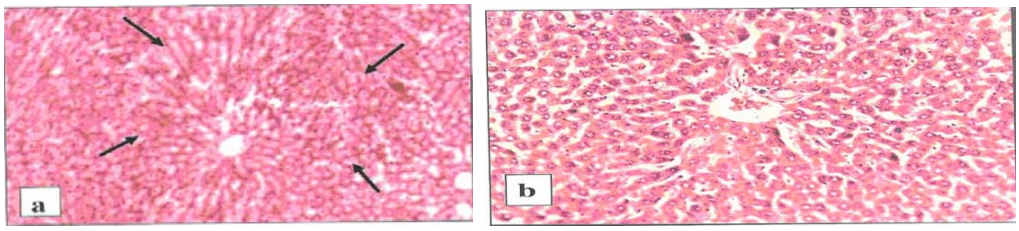

Fig. (1). a) Liver of control, untreated rat showing the normal histological structure of hepatic lobule. (H and E X 200). **b**) Liver of rat treated with taurine 1000 mg/kg body weight/day showing normal architecture of hepatic lobule. (H and E X 400).

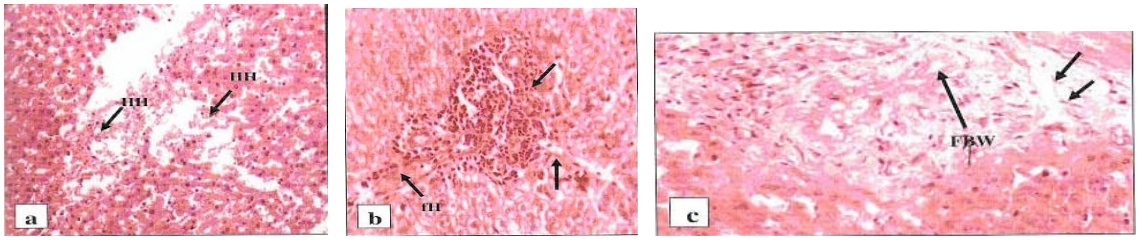

Fig. (2). a) Liver of rat treated with MSG 400mg/kg body weight/day for one month showing hepatic haemorrhage (HH) dispersed the hepatocytes from each other. (H and E X 200). **b**) Liver of rat treated with MSG 400mg/kg body weight/day for one month showing focal haemorage (FH) as well as necrosis of hepatocytes with pyknotic nuclei. (H and E X 200). **c**) Liver of rat treated with MSG 400mg/kg body weight/day for one month showing fibrosis of bile duct wall (FBW). (H and E X 200).

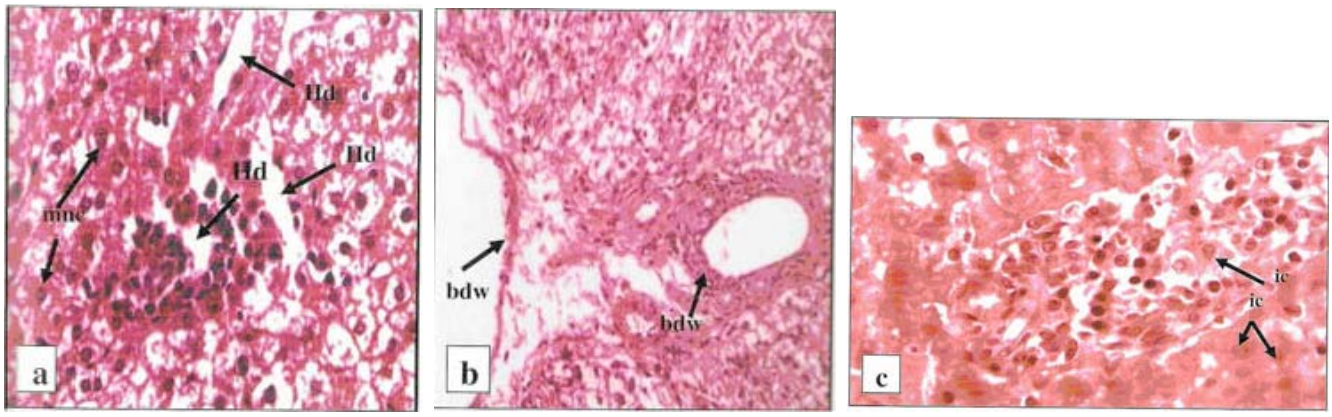

Fig. (3). a) Liver of rat treated with MSG 400mg/kg body weight/day for two months showing hydrobic degeneration (Hd) of hepatocytes as well as focal hepatic necrosis replaced by mononuclear cells infiltration (mnc). (H and E X 400). **b**) Liver of rat treated with MSG 400mg/kg body weight/day for two months showing portal edema and thickening in the wall of bile duct (bdw). (H and E X 200). **c**) Liver of rat treated with MSG 400mg/kg body weight/day for two months showing portal infiltration with mononuclear inflammatory cells (ic). (H and E X 400).

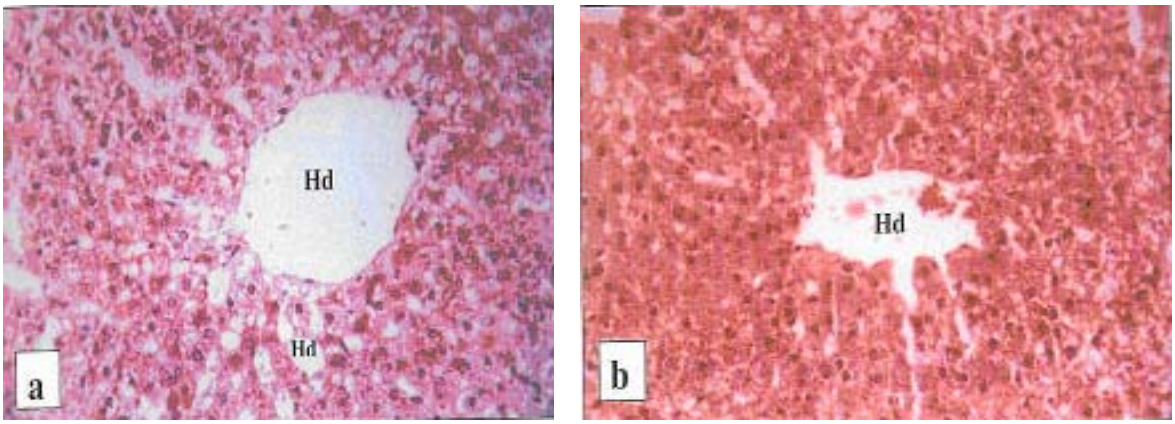

Fig. (4). a) Liver of rat treated with MSG 400mg/kg body weight/day then with taurine 1000 mg/kg body weight/day for two months (therapeutic) showing hydrobic degeneration (Hd) of hepatocytes. (H and E X 200). **b**) Liver of rat treated with taurine 1000 mg/kg body weight/day then with MSG 400mg/kg body weight/day for two months(protective) showing slight hydrobic degeneration (Hd) of few hepatocytes. (H and E X 200).

The ultrastructural examination of (Fig. **5**) shows normal hepatocytes with round nucleus, different shapes of mitochondria, and clear cytoplasm with normal endoplasmic reticulum (E. R.).

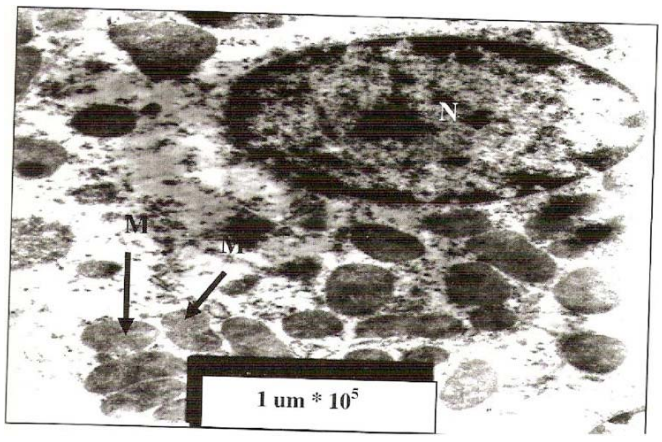

Fig. (5). Part of normal hepatocyte with round nucleus (N). there were different shapes of mitochondria (M).

At the same time, the treatment for 8 weeks lead to different ultra structural changes has been occurred, such as the ultra structural examination in MSG group after 8 weeks showed areas of hyaline degeneration (fatty) of the cytoplasm. Few organelles and few E. R, cytoplasm were rich in glycogen granules, while membranes were slightly irregular with normal cytoplasm and few degenerated areas. The same group showed rounded nucleus, rounded mitochondria, and few cistern of rough E. R. and stage of mitotic figure, where nuclear membrane lost (Fig. **6a-e**).

While the hepatocyte examined by EM in therapeutic groups after 8 weeks showed mitochondria and endoplasmic reticulum, and hyaline degeneration of cytoplasm (Fig. **7a**), normal nucleus and mitochondria (Fig. **7b**) and the reticulate cell showed few organelle and degenerated cytoplasm, normal nucleus, mitochondria and rough E. R. (Fig. **7c**), small areas of hyaline degeneration (possible dissolved glycogen), rounded nucleus mitochondria (Fig. **7d**), fatty degeneration in between the mitochondria and cistern of rough E. R. (Fig. **7e**).

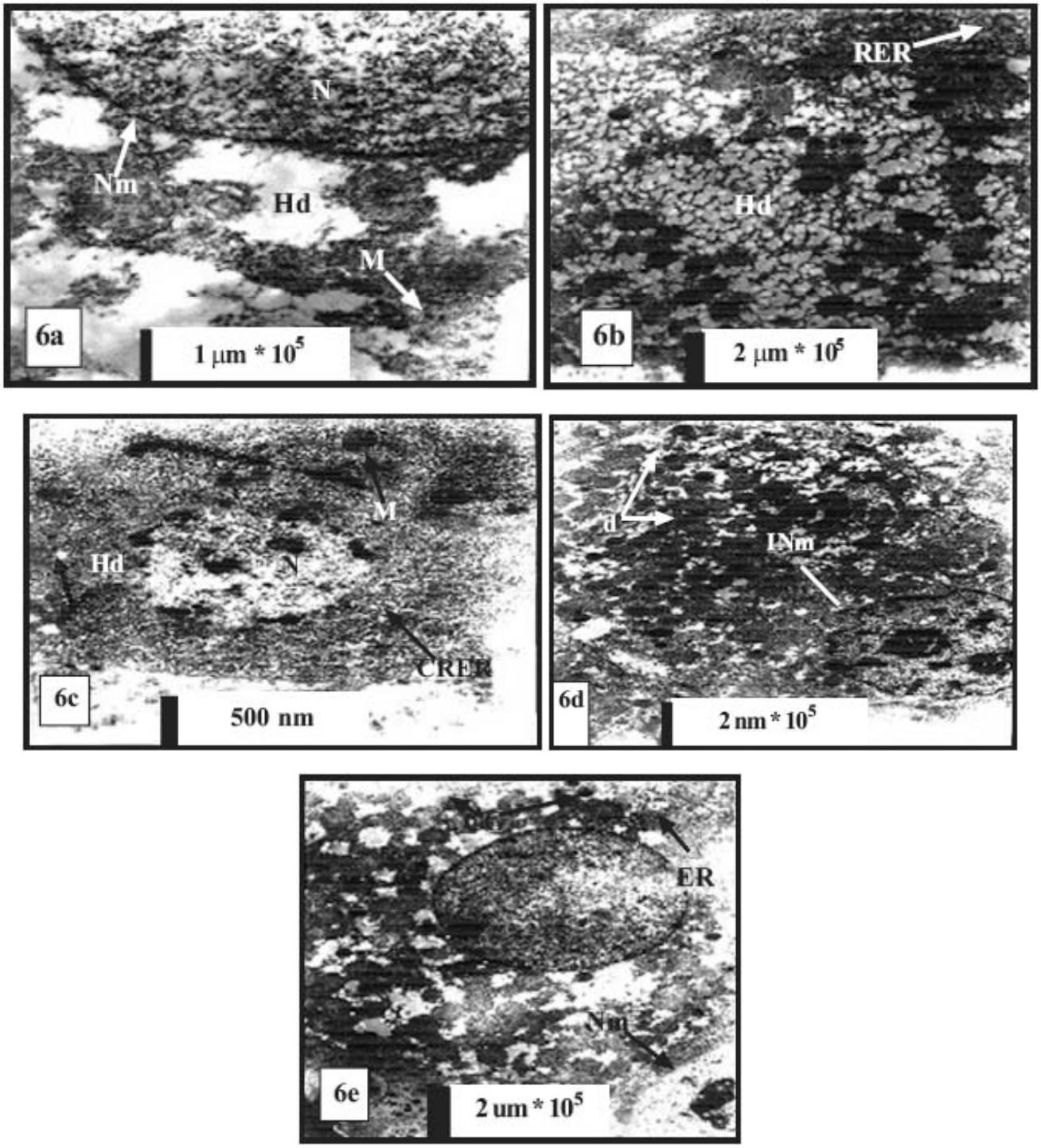

Fig. (6). (a). Part of hepatocyte of liver of a rat treated with MSG 400mg/kg body weight/day for two months shows nucleus (N) with typical nuclear membrane (Nm). The cytoplasm shows rounded mitochondria with typical mitochondria cristea (M). Areas of hyaline degeneration (fatty) of the cytoplasm are appeared (Hd). **(b).** Part of cytoplasm of liver of a rat treated with MSG 400mg/kg body weight/day for two months shows few organelles**.** Hyaline degeneration of the cytoplasm (Hd) and few Rough Endoplasmic Reticulum (R.E.R) are appeared. **(c).** hepatocyte of liver of a rat treated with MSG 400mg/kg body weight/day for two months shows round nucleus (N) rounded mitochondria (M), areas of hyaline or fatty degeneration(Hd) and few cistern of rough endoplasmic reticulum (CRER).**(d).** Part of hepatocyte of a rat treated with MSG 400mg/kg body weight/day for two months shows slightly irregular nuclear membrane (INm). Normal cytoplasm with few degenerated areas appeared (d). **(e).** Part of hepatocyte of a rat treated with MSG 400mg/kg body weight/day for two months in stage of mitotic figure where nuclear membrane lost (Nm). Also the cytoplasm rich in glycogen granules (GG) and few Endoplasmic Reticulum (ER).

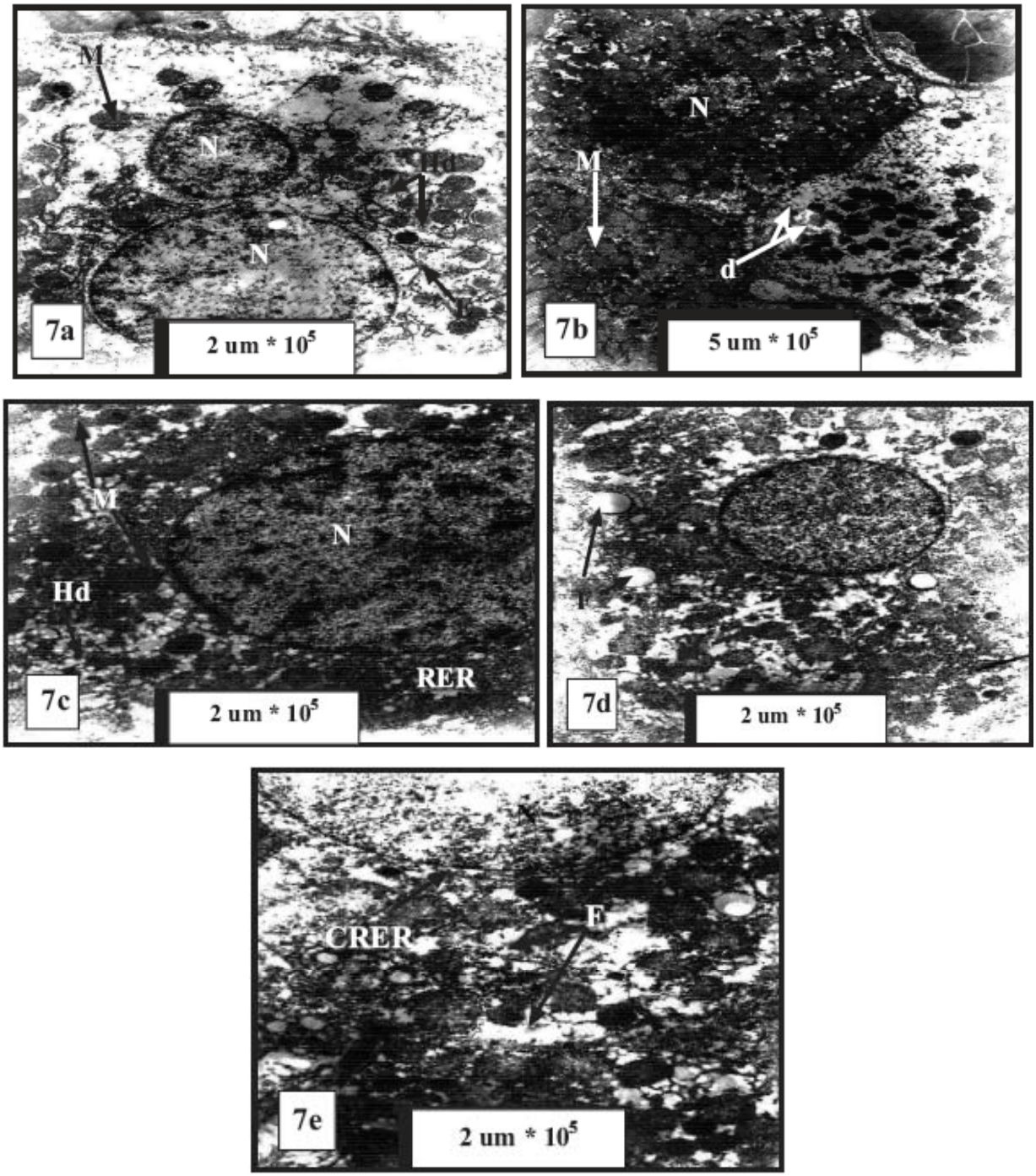

Fig. (7). (a). Part of binucleated hepatocyte N(normal nuclei) of a rat treated with MSG 400mg/kg body weight/day then with taurine 1000 mg/kg body weight/day for two months shows few mitochondria (M) There was Endoplasmic Reticulum (ER) hyaline degeneration of cytoplasm (Hd). **(b).** Three adjacent hepatocyte of a rat treated with MSG 400mg/kg body weight/day then with taurine 1000 mg/kg body weight/day for two months.two normal shows normal nucleus (N) and mitochondria (M). The cell shows few organelle and degenerated cytoplasm (d). **(c).** Part of hepatocyte of a rat treated with MSG 400mg/kg body weight/day then with taurine 1000 mg/kg body weight/day for two months shows normal nucleus (N), mitochondria (M) and Rough Endoplasmic Reticulum (R.E.R). There are small areas of hyaline degeneration (Hd), possible dissolved glycogen. **(d).** Hepatocyte of a rat treated with MSG 400mg/kg body weight/day then with taurine 1000 mg/kg body weight/day for two months shows rounded nucleus (N), fat globules at cytoplasm (F). Normal rounded mitochondria (M). **(e).** Hepatocyte of a rat treated with MSG 400mg/kg body weight/day then with taurine 1000 mg/kg body weight/day for two months shows normal nucleus (N). Fatty degeneration (F) in between the mitochondria and cistern of rough endoplasmic reticulum (CRER).

Interestingly, the ultra structural examination of the protective group after two months showed large rounded nucleus, normal mitochondria with normal cristae and normal rough E. R. (Fig. **8a**), few lysosomes (Fig. **8b**), cyto-

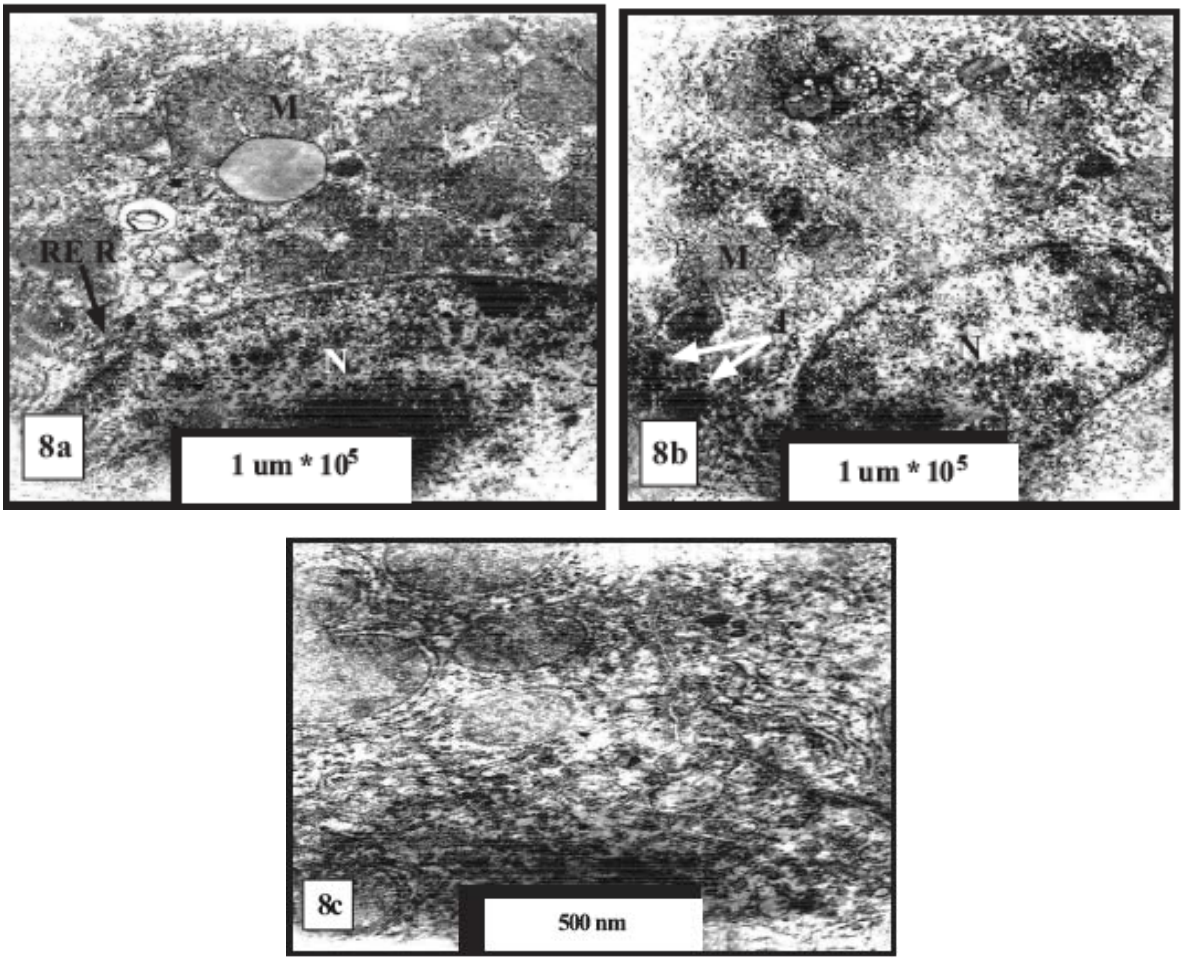

Fig. (8). (a). Part of hepatocyte of rat treated with taurine 1000 mg/kg body weight/day then with MSG 400mg/kg body weight/day for two months with large rounded nucleus (N). There were normal mitochondria with normal cristae (M). Also rough endoplasmic reticulum (R.E.R) was normal. **(b).** Part of hepatocyte of rat treated with taurine 1000 mg/kg body weight/day then with MSG 400mg/kg body weight/day for two months shows normal hepatocyte, normal nucleus (N), normal mitochondria (M) and few lysosomes (L). **(c).** Part of hepatocyte of rat treated with taurine 1000 mg/kg body weight/day then with MSG 400mg/kg body weight/day for two months shows normal hepatocyte. The cytoplasm appear normal.

plasm with normal appearance and normal appearance of cistern of rough E. R. (Fig. **8c**).

DISCUSSION

MSG is widely used as a food additive to improve the taste of food, because it potentiates the activity of gustatory nerve [17]. In particular, this nerve mediate sweet taste [18].

Regarding to hepatotoxic effect of MSG the result showed gradual elevation ($P<0.01$) in the serum levels of liver enzymes and bilirubin, which exhibited a value four times higher than normal after 8 weeks. This confirms the cumulative adverse effect of MSG. Moreover, hydropic degeneration of hepatocyte, focal hepatic necrosis, portal edema, focal hemorrhage, necrosis and fibrosis of bile ducts all these histopathological disfigurement were also observed Fig. (**2-4**) when compared with control and rats treated with taurine only (Fig. **1**). Concomitantly, the ultra structural examination for the same group showed hyaline degeneration of the cytoplasm, few endoplasmic reticulum and irregular nuclear membrane which may lost in some figures after 8 weeks.

Confirming our observation, I noticed that MSG administration initially attacked the peripheral hepatocytes in the central lobules of the liver tissues leading to hepatocellular degeneration [19]. Recently, calcium level increased in liver by administrating MSG to adult male mice [20]. The authors revealed this condition to the increase in oxidative stress effect. An increased intracellular concentration of Ca^{+2} could theoretically act either to enhance lipid peroxidation or to stimulate degeneration of phospholipids. Similarly hepatocellular damage with elevation of all serum liver enzymes was observed [21-23] after ingesting the rat with MSG. Concomitantly, it was attributed with the histopathological and ultrastructural change in rats live treated with MSG to the accumulation of highly reactive and cytotoxic intermediate, which may cause centribular necrosis of hepatocyte [2, 24-26]. In conclusion, reactive oxygen species, lipid peroxi-

dation and disordered Ca^{+2} homeoestasis are the mechanisms that may have contributory role in the development of liver injury after MSG excess.

On the other hand, administration at taurine before MSG (Therapeutically) resulted in a significant restore of hepatic injury as evidenced by attenuation and hepatocellular enzymes and bilirubin release and reduction of hepatocyte necrosis with slight hydropic degeneration of few hepatocyte.

Same observations were postulated that therapeutic administration of taurine after the hepatotoxic substance elevated the intracellular taurine, that increase the ability to protect against oxidant-induced hepatotoxicity through its cytoprotective effect [27]. The most interesting point in this work is the normal restore of liver enzymes and bilirubin release accompanied with its normal histological and ultrastructural architecture and hepatocyte in the group of rats treated with taurine before MSG (protectively) [28]. In conclusion, when taurine was used protectively (12 h before the oxidant treatment) noticed normalization in plasma level of AST, ALT and ALK and disappearance of hepatocyte necrosis [28]. Lastly, taurine can protect the hepatocyte against MSG, through different mechanisms included cell membrane stabilization [9, 24], antioxidation and detoxification [27-30], osmoregulation [29, 31-33], neuromodulation [34] and regulation of Ca^{+2} homeostasis [27, 35, 36].

In conclusion, on the basis of these findings we advise to add a suitable dose of taurine to any food containing MSG as a food addictive, because there is no doubt that taurine is considered as powerful hepatoprotective substance that can protect the hepatocyte through different mechanisms.

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