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# Neonatal Monosodium Glutamate Administration Modifies Liver Histology and Stereological Parameters in Sprague Dawley Rats

## La Administración Neonatal de Glutamato Monosódico Modifica la Histología Hepática y los Parámetros Estereológicos en Ratas Sprague Dawley

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**SUMMARY:** Monosodium glutamate (MSG) is one of the most widely used food additives due to its flavor-enhancing properties. Experimental studies have suggested that chronic exposure to MSG may induce metabolic disturbances and structural alterations in several organs, particularly the liver. The aim of this study was to determine the effects of neonatal MSG administration on liver morphology and hepatocyte stereological parameters in Sprague-Dawley rats. Neonatal rats were distributed into control and experimental groups receiving subcutaneous MSG administration. Animals were maintained under standard laboratory conditions for up to 16 weeks. Liver samples were collected after euthanasia and processed for histological analysis using hematoxylin-eosin staining. Qualitative and quantitative stereological evaluations were performed, including volume density (Vv), surface density (Sv), and numerical density (Na) of hepatocytes. MSG-treated animals exhibited histological alterations characterized by parenchymal disorganization, sinusoidal dilation, inflammatory infiltration, increased adipose tissue deposition, and signs of fibrosis. Furthermore, significant reductions in stereological parameters were observed compared with controls ($p<0.05$). These findings suggest that neonatal MSG exposure induces persistent hepatic morphological alterations that may contribute to the development of metabolic-associated liver injury.

**KEY WORDS: Monosodium glutamate; Liver; Stereology; Liver fibrosis; Hepatocytes.**

## INTRODUCTION

Monosodium glutamate (MSG) is the sodium salt of glutamic acid, an amino acid naturally present in various foods and widely used by the food industry as a flavor enhancer for *umami* (Jinap & Hajeb, 2010). Due to its extensive use in processed products and industrially prepared foods, it is one of the most widely consumed food additives worldwide.

Various studies have suggested an association between prolonged exposure to MSG and metabolic alterations linked to obesity, insulin resistance, and metabolic syndrome. It has been proposed that MSG induces lesions in hypothalamic nuclei involved in the regulation of appetite and energy balance, thereby promoting the development of visceral obesity and endocrine alterations (Carbonero-Carreño, 2013; Niaz *et al*., 2018).

MSG-induced metabolic alterations could affect multiple organs, particularly the liver. Experimental studies have described central vein dilation, cytoplasmic vacuolization, inflammatory infiltration, hepatocyte necrosis, and lipid droplet accumulation in animals exposed to the compound (Waer & Edress, 2006; Eweka *et al*., 2011; Othman & Bin-Jumah, 2019). Furthermore, MSG-induced obesity models have shown histopathological changes consistent with non-alcoholic fatty liver disease, including steatosis and lobular inflammation (Tsuneyama *et al*., 2014; Belemets *et al*., 2016).

Although there is existing evidence regarding the hepatotoxic effects of MSG, few studies have quantified these alterations using stereological tools. Therefore, the aim of this study was to evaluate the hepatic histological

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and stereological changes induced by neonatal MSG administration in Sprague-Dawley rats.

## MATERIAL AND METHOD

### Experimental design

An experimental study was conducted using 18 neonatal Sprague-Dawley rats obtained from the Center of Excellence in Morphological and Surgical Studies (CEMyQ) at the University of La Frontera, Temuco, Chile. The animals were housed at a temperature of 22 ± 2°C and a relative humidity of 50–70%, under 12-hour light-dark cycles, with free access to water and a standard AIN-93M diet. The animals were assigned to control and experimental groups. The control group (n=6) received a subcutaneous injection of 0.9% saline solution. The experimental groups received a subcutaneous injection of monosodium glutamate at a dose of 4 mg/g of body weight during the neonatal period. Subsequently, the animals were maintained for periods of up to 8 (MSG1) and 16 weeks (MSG2) and then euthanized via intraperitoneal administration of sodium pentobarbital (150–200 mg/kg). The study was approved by the Scientific Ethics Committee of the Universidad de La Frontera (No. 051/2017).

### Histological processing

Following euthanasia, the livers were removed, and their volume was determined using the Scherle method. The samples were fixed in 4 % buffered formalin, processed using standard histological techniques, and embedded in paraffin. Histological sections (5 µm thick) were prepared and stained with hematoxylin-eosin for microscopic evaluation.

### Stereological analysis

Images were obtained using a Leica DM750 light microscope. Stereological analysis was performed using STEPanizer® software. The following parameters were determined: volume density (Vv), surface density (Sv), and numerical density (Na).

### Statistical analysis

Data were analyzed using IBM SPSS Statistics software (version 29). Differences between groups were evaluated using analysis of variance (ANOVA) followed by Tukey's post hoc test. A p-value < 0.05 was considered significant.

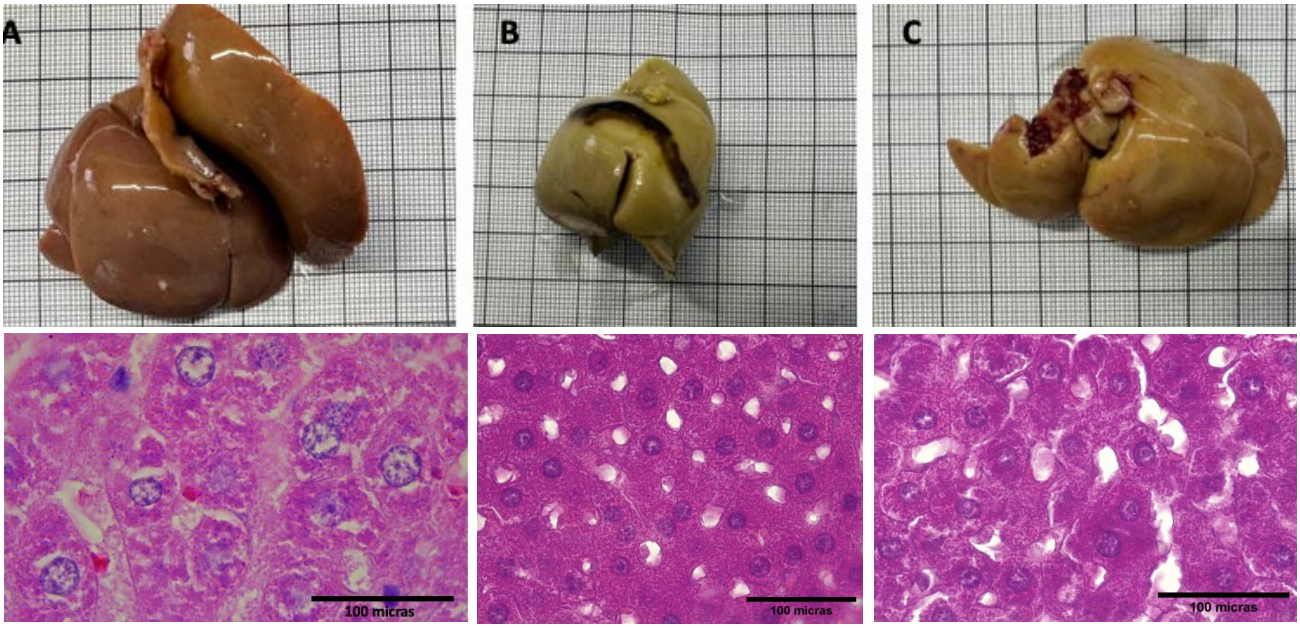



Fig. 1. Liver diameter in the study groups. A) CG; B) MSG1; and C) MSG2. Note the difference in liver coloration among the respective groups, attributable to the increase in adipose tissue in the experimental groups. Hepatic parenchyma of groups: control D and exposed to MSG: in groups E (MSG1), tissue disorganization is observed; in groups F (MSG2), an increase in sinusoidal capillary diameter are observed. 100X. H&E stain.

## RESULTS

### Macroscopic evaluation

Livers obtained from animals exposed to MSG appeared paler than those of the control group; an apparent increase in adipose content was also observed, particularly in animals subjected to longer periods of exposure (Fig. 1).

### Histological analysis

The control group exhibited normal histological organization of the hepatic parenchyma, with hepatocytes arranged in regular cellular cords and no evidence of inflammatory infiltration. In contrast, the groups treated with GMS showed progressive structural alterations characterized by disorganization of the hepatic parenchyma, loss of normal lobular architecture, increased sinusoidal capillary diameter, and the presence of inflammatory infiltrate. In animals with longer exposure times, areas consistent with early-stage fibrosis and increased intrahepatic adipose tissue were observed (Fig. 1).

### Stereological analysis

Stereological parameters showed a progressive decrease in the GMS-exposed groups compared to the control group. Volume density (Vv) decreased from 60.12% in the control group to 40.48 % and 18.00 % in the GMS1 and GMS2 groups, respectively. Surface density (Sv) decreased from 20.00 in the control group to 15.05 in GMS1 and 10.38 in GMS2. Furthermore, numerical density (Na) showed values of 164.74 in the control group, 124.31 in GMS1, and 102.04 in GMS2. All variables showed statistically significant differences among the groups studied ($p<0.05$) (Fig. 2 and Table I).

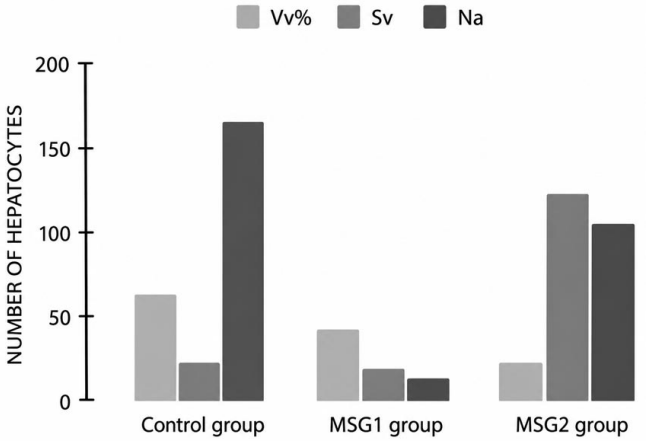



Fig. 2. Stereology demonstrates hepatic fibrosis *vs.* number of hepatocytes in the control group.

## DISCUSSION

The results of the present study demonstrate that neonatal administration of monosodium glutamate (MSG) induces significant alterations in hepatic architecture, evidenced by parenchymal disorganization, inflammatory infiltration, increased adipose tissue, and a decrease in the stereological parameters Vv, Sv, and Na. These findings suggest that early exposure to MSG causes persistent modifications in hepatic structure, consistent with processes of metabolic damage and tissue remodeling.

In recent years, various experimental studies have confirmed the ability of MSG to induce hepatic histopathological alterations associated with oxidative stress and inflammation. Sahin *et al*. (2023), observed marked disorganization of hepatic cords, vascular congestion, inflammatory infiltration, and hepatocyte degeneration in MSG-treated rats, accompanied by biochemical alterations linked to oxidative damage. The authors proposed that oxidative stress is a primary mechanism underlying MSG-induced hepatotoxicity. The findings described in that study are consistent with the histological alterations observed in the experimental groups of the present research.

The observed disorganization and alterations may be attributed to an imbalance between the production of reactive oxygen species and hepatic antioxidant mechanisms—alterations demonstrated during chronic exposure to MSG, as seen in our model. Thangachi *et al*. (2021),reported a significant increase in lipid peroxidation markers alongside alterations in hepatic antioxidant enzymes in rats exposed to varying doses of MSG, concluding that the compound creates an oxidative microenvironment capable of compromising the liver's structural integrity. This

Table I. Summary of stereological parameters of hepatic tissue. A decrease in hepatocyte volume density (Vv), surface density (Sv), and numerical density (Na) is observed in groups MSG1 and MSG2.

| Rats n=18 | Control Group (CG) | MSG1 Group | MSG2 Group | DE P<0.05 |
|---|---|---|---|---|
| Vv | 60.12 % | 40.48 % | 18 % | 0.03 |
| Sv | 20 | 15,05 | 10.38 | 0.04 |
| Na | 164.74 | 124.31 | 102.04 | 0.04 |

mechanism could partially explain the reduction in hepatocyte volumetric and numerical density observed in the treated groups in the present study.

Another significant finding was the presence of intrahepatic adipose tissue and signs consistent with fibrosis in animals exposed for longer periods. In this context, Abd-Elkareem *et al.* (2022), demonstrated that GMS administration causes hepatic alterations characterized by hepatocellular degeneration, lipid accumulation, and increased connective tissue—changes attributed to persistent inflammatory processes and the activation of profibrotic mechanisms. The authors suggest that chronic oxidative stress triggers cellular responses that promote extracellular matrix deposition and progression toward hepatic fibrosis. The findings observed in our study are consistent with this interpretation.

The progressive decline in the stereological parameters Vv, Sv, and Na observed in the GMS1 and GMS2 groups represents one of the key contributions of this research. Although most recent studies have focused on conventional biochemical or histopathological parameters, there is growing evidence that metabolic alterations associated with oxidative stress lead to a loss of functional hepatocyte mass and modifications to the three-dimensional organization of hepatic tissue. In this regard, recent research has indicated that sustained oxidative damage impairs cell viability, promotes apoptosis, and affects the regenerative capacity of hepatocytes, resulting in structural changes detectable through morphometric and stereological analyses.

The role of inflammation and oxidative stress as central mechanisms in MSG-induced toxicity has been reinforced (Adebayo *et al*., 2024). Experimental models have demonstrated that exogenous exposure to the compound significantly increases the production of inflammatory mediators and reactive oxygen species, thereby exacerbating tissue damage and promoting persistent structural alterations. Although these studies were conducted primarily on nervous tissue, the described cellular mechanisms are consistent with those observed in the liver and could help explain the morphological alterations found in the present study.

Overall, the evidence supports the hypothesis that neonatal exposure to MSG induces a cascade of pathophysiological events characterized by oxidative stress, chronic inflammation, lipid accumulation, and progressive tissue remodeling. The results of this study extend these findings by incorporating a quantitative stereological assessment, demonstrating that these alterations affect not only general hepatic histology but also the three-dimensional organization and density of hepatocytes. Therefore, the experimental model used serves as a useful tool for studying the early mechanisms involved in the development of liver diseases associated with MSG-induced metabolic disorders.

## CONCLUSION

Neonatal administration of monosodium glutamate significantly alters hepatic histology in Sprague-Dawley rats. Exposed animals exhibit disorganization of the hepatic parenchyma, inflammatory infiltration, increased adipose tissue, and signs consistent with fibrosis. The stereological parameters Vv, Sv, and Na decrease significantly following MSG exposure, indicating quantitative and structural alterations in hepatocytes. These findings support the hypothesis that monosodium glutamate can induce progressive liver damage and contribute to the development of hepatic metabolic abnormalities.

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**RESUMEN:** El glutamato monosódico (GMS) es uno de los aditivos alimentarios más utilizados en la industria alimentaria debido a su capacidad para potenciar el sabor umami. Diversos estudios experimentales han sugerido que su administración prolongada podría generar alteraciones metabólicas y cambios estructurales en distintos órganos, particularmente en el hígado. El objetivo del presente estudio fue determinar los efectos de la administración neonatal de GMS sobre la morfología hepática y los parámetros estereológicos de hepatocitos en ratas Sprague-Dawley. Se utilizaron ratas neonatas distribuidas en un grupo control y grupos experimentales tratados con GMS mediante administración subcutánea. Los animales fueron mantenidos con dieta estándar durante períodos de hasta 16 semanas. Posteriormente se realizó eutanasia, extracción hepática, procesamiento histológico y tinción con hematoxilina-eosina. Se evaluaron parámetros cualitativos y cuantitativos mediante análisis estereológico, incluyendo densidad de volumen (Vv), densidad de superficie (Sv) y densidad numérica (Na) de hepatocitos. Los grupos tratados con GMS mostraron alteraciones histológicas caracterizadas por desorganización del parénquima hepático, aumento del diámetro sinusoidal, infiltración inflamatoria, incremento del tejido adiposo y signos compatibles con fibrosis. Asimismo, se observó una disminución significativa de los parámetros estereológicos respecto al grupo control ($p<0,05$). Los hallazgos sugieren que la exposición neonatal al GMS induce cambios morfológicos hepáticos persistentes que podrían favorecer el desarrollo de daño hepático asociado a alteraciones metabólicas.

**PALABRAS CLAVE: Glutamato monosódico; Hígado; Estereología; Fibrosis hepática; Hepatocitos.**

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