Monosodium Glutamate Alters the Function and Morphology of the Parotid Gland in Sprague Dawley Rats

Glutamato Monosódico Altera la Función y Morfología de la Glándula Parótida en Ratas Sprague Dawley

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SUMMARY: Monosodium glutamate (MSG) is a flavor enhancer widely used in the food industry, with obesogenic properties, in addition to causing alterations in the oral cavity. The aim of the study was to observe the morphofunctional changes in the parotid gland after the administration of MSG in rats. 18 newborn male Sprague Dawley rats were used, divided into three groups (Control group; MSG1 group: 4 mg/g weight of monosodium glutamate, 5 doses, kept for 8 weeks, and MSG2 group: 4 mg/g weight of MSG, 5 doses, kept for 16 weeks). The body mass index (BMI) was calculated, and the salivary flow, pH, α-amylase activity, Na, Cl, K and Ca were analyzed by quantitative analysis. After euthanasia by ketamine/xylazine overdose, parotid volume was analyzed and stereology was performed. MSG administration caused an increase in BMI and a decrease in parotid volume as well as a reduction in salivary flow and pH and an increase in α-amylase activity, also increasing the salivary sodium and chlorine levels. Alterations in the normal stereological parameters of the gland were observed. Exposure to MSG caused morphofunctional alterations at parotid gland.

KEY WORDS: Monosodium glutamate; Saliva; Parotid gland; Salivary flow; pH; α-amylase.

INTRODUCTION

The obesogenic properties of monosodium glutamate (MSG) have been studied by various authors (Bunyan et al., 1976; Baculiikova et al., 2008; Miranda et al., 2017), observing that its ingestion may be associated with the increased risk of overweight regardless of physical activity and total energy consumption in humans (He et al., 2008; Beregova et al., 2014). It is also associated with insulin resistance (Hirata et al., 1997) and hyperinsulinemia (Marmo et al., 1994) in obesity models in rats, as well as increased adiposity and obesity (Dolnikoff et al., 2001).

At the systemic level, the harmful effect of MSG has been reported in several structures, such as the central nervous system, fatty tissue, liver, digestive tract and reproductive organs, among others (Collison et al., 2010a; Husarova & Ostatnikova, 2013, López-Miranda et al., 2015) On the other hand, obesity has been linked to various alterations in the oral cavity, such as caries, periodontitis and xerostomia (Barreto Villela et al., 2004; Saito et al., 2005, Mathus-Vliegen et al., 2007; Flink et al., 2008; Ueda et al., 2013, Salamonowicz et al., 2019).

The existing literature on the relation between obesity and salivary glands is still scarce, concentrating mainly on its effects on the functional activity of the glands (Inoue et al., 1977; Renzi et al., 1989; Mozaffari et al., 2011; Zalewska et al., 2014), with the likely structural changes at glandular level still being poorly documented. The aim of the study was to observe the morphofunctional changes in the parotid gland after the administration of MSG in rats.

MATERIAL AND METHOD

Animals and Experimental Protocol. Eighteen newborn male Sprague Dawley rats were used (2 days old). At the beginning of the experimental period (day 1), the rats were divided into three groups: Control group (n=6) exposed to saline solution (sodium chloride 0.9 % (p/v) in distilled water) 8 ml/g administered subcutaneously. MSG1 group: (n=6) exposed to subcutaneous MSG, 4 mg/g weight two doses, 2nd and 4th day and 2 mg/g weight, 6th, 8th, 10th day doses.
Parotid gland stereological analysis. Once the parotid glands had been obtained, they were fixed in buffered formalin (1.27 mol/l of formaldehyde in phosphate buffer 0.1 M pH 7.2) for 48 h, dehydrated and embedded in Paraplast Plus (Sigma-Aldrich Co., St. Louis, MO, U.S.A.). Once the blocks were obtained, 5 sections were made, 5 mm thick (Leica® RM2255), and stained with H&E.

Five fields were observed for each section; in total 125 fields per group. The slides were observed under an optical microscope (Leica®, DM750, Switzerland) with integrated camera (Leica® ICS50W, Nussloch, Germany) and the images were projected onto a flat screen monitor (View Sonic®). The analyzed parameters were: adenomere volume density ($V_{vad}$), adenomere surface density ($S_{vad}$) and adenomere area density ($NA_{vad}$) measured using the multipurpose test system M42 (Mandarim-de-Lacerda & del Sol, 2017). This same sequence was applied to the system multipurpose test system M42 (Mandarim-de-Lacerda & del Sol, 2017). This same sequence was applied to the system multipurpose test system M42 (Mandarim-de-Lacerda & del Sol, 2017). This same sequence was applied to the system multipurpose test system M42 (Mandarim-de-Lacerda & del Sol, 2017). This same sequence was applied to the system multipurpose test system M42 (Mandarim-de-Lacerda & del Sol, 2017). This same sequence was applied to the system multipurpose test system M42 (Mandarim-de-Lacerda & del Sol, 2017). This same sequence was applied to the system multipurpose test system M42 (Mandarim-de-Lacerda & del Sol, 2017).

RESULTS

MSG caused increased BMI and reduced parotid volume. Upon completion of the experimental period, an increase in the rats’ BMI was observed in both the MSG1 and MSG2 groups compared to the control group, results which were not statistically significant. With respect to the parotid volume, it presented a decrease in the MSG1 group ($0.16±0.9 cm^3$) and MSG2 group ($0.27±0.06 cm^3$) compared to the control group ($0.52±0.19 cm^3$), which was statistically significant ($p=0.0014$).

MSG caused a decrease in pH levels, salivary flow and an increase in a-amylase, as well as changes in the percentages of salivary elements.
After the experimental period, the rats in the MSG1 and MSG2 groups showed a reduction in salivary pH, MSG1 (8.4±0.48), MSG2 (7.7±0.23) and control (8.8±0.36), a statistically significant result (p=0.0009) for MSG2. The salivary flow rates by group were: control (33.5±9.29 mL/min), MSG1 (20.3±1.3 mL/min) and MSG2 (19.3±6.4 mL/min), with a decrease in the MSG1 and MSG2 groups being noted - statistically significant results (p=0.003). The α-amylase presented increases in the MSG1 (16579±7223 U/L) and MSG2 groups (11732±3999 U/L) compared to the control group (5905±1688 U/L), significant only for the control group /MSG1 (p=0.0073).

The values for the elements determined in the saliva appear in Table I. Exposure to MSG induced changes in salivary electrolytes, there being statistically significant differences in the increases in sodium in both the MSG1 (5.47±2.44) and MSG2 (5.18±1.79) groups compared to the control (3.78±1.79) (p=0.0002). In the same way, the chloride presented statistically significant increases (p< 0.0001) in both the MSG1 and MSG2 groups compared to the control group. The potassium and calcium showed slight reductions in the MSG1 and MSG2 groups compared to the control group, results that were not statistically significant (p= 0.0890 and 0.2805 respectively).

Table I. Salivary elementary semiquantitative microanalysis of male Sprague Dawley rat subjected to MSG.

| Mass percent (%) | Groups | Control | MSG1 | MSG2 | p       |
|------------------|--------|---------|------|------|---------|
| Na               |        | 3.78±1.89 | 5.47±2.44 | 5.18±1.79 | 0.0002  |
| Cl               |        | 14.17±4.78 | 17.44±5.8  | 19.85±6.98 | < 0.0001|
| K                |        | 13.3±5.08  | 10.96±4.67 | 12.20±4.33 | 0.0890  |
| Ca               |        | 3.25±3.64  | 1.77±1.93  | 1.45±0.78  | 0.2805  |

a: Dif. sig. control/MSG1 (p=0.005), según análisis de ANOVA.
b: Dif. sig. control/MSG2 (p=0.005), según análisis de ANOVA.
c: Dif. sig. control/MSG2 (p=0.05), según análisis de ANOVA.
d: Dif. sig. control/MSG2 (p< 0.0001), según análisis de ANOVA.

Fig. 1. Effects of MSG on BMI and parotid volume in rats exposed for 8 and 16 weeks and control group. A: MSG increases the BMI, time-dependent. B: MSG reduces parotid volume.

Fig. 2. Effects of MSG on pH, salivary flow and α-amylase activity in rats exposed for 8 and 16 weeks and control group. A: MSG reduces salivary pH. B: MSG reduces salivary flow. C: MSG increases α-amylase activity.
MSG caused changes in the stereological parameters. The stereological analysis reflected a reduction in adenomere Vv, Sv and NA of the parotid gland in the MSG1 and MSG2 groups, statistically significant values (p<0.001, <0.001 and 0.0099 respectively) compared to the control group. On the other hand, the Vv and Sv of the striated ducts of the parotid gland in the MSG1 and MSG2 groups decreased in comparison with the control group (p<0.001). The total ducts showed a decrease in Vv, NA and Sv, with the last one presenting statistically significant differences (p<0.001). The parameter of the Nv of adenomere cells showed a reduction for both the MSG1 and MSG2 groups compared to the control group, a statistically significant result for MSG2 (p=0.0024).

**DISCUSSION**

MSG is the sodium salt of glutamate, an amino acid found naturally in multiple foods (Jinap & Hajeb, 2010; Behrens et al., 2011) and which is currently a widely consumed food additive (Shi et al.). According to Von Diemen et al. (2006), the administration of MSG in newborn rats causes the destruction of the hypothalamic ventromedial and arcuate nuclei, with these animals later developing obesity due to the lack of control between absorption and energy expenditure. In addition, changes to the central nervous system, fatty tissue, liver and reproductive organs have been reported (Husarova & Ostatnikova), as well as in the oral structures (Beregova et al.; Hordiienko et al., 2014).

The administration of MSG in the rats in the experimental groups induced greater weight gain than in the rats in the control group, reflected in an increased BMI; this
increase is related to the exposure time: the greater the exposure time to MSG, the higher the BMI. Previous studies indicate that MSG consumption produces a significant increase in body weight, both in animal models and in humans (Abd El–Aziz et al., 2014; Collison et al., 2010b; He et al., 2008, 2011; Insuwang et al., 2012; Matysková et al., 2008). Iwase et al. (2000) describe obesity and the increase in food ingestion as being related to the increase in leptin resistance in the arcuate nucleus, which is damaged by the action of MSG (Von Diemen et al.).

Although the association of MSG with the increased risk of overweight has been widely reported, the data obtained from studies on humans or experiments on animals is controversial and has not been fully confirmed (Ebert, 2009). Kondoh & Torii (1995) indicated that MSG suppresses weight increase, fat deposition and leptin levels in Sprague-Dawley rats. Similarly, Shi et al. (2010) reported that MSG ingestion was not associated with a greater prevalence of obesity or with a clinically significant weight increase in Chinese adults.

MSG administration decreased the parotid volume in the experimental groups compared to the animals who did not receive it, a decrease possibly associated with the MSG administration period. An exposure of 8 weeks (MSG1) induced a greater reduction in the parotid volume (0.16±0.9 cm³) than in the MSG2 group induced for 16 weeks (0.27±0.06 cm³), which indicated that the parotid gland could partially recover its volume, although not achieving normality. Although there are no records of a volume/obesity association, there is evidence between the reduction in the weight of the salivary glands in rats and obesity induced by hypothalamic damage (Inoue et al.), induced by neonatal administration of MSG. In addition, pathologies like diabetes induce changes in the weight of the salivary glands; Ibuki et al. (2010) demonstrated a significant reduction in the mass of the submandibular gland in diabetes induced in rats. Other authors have reported atrophy of the parotid and submandibular glands accompanied by a degeneration of the acinus (Takai et al., 1983; Anderson et al., 1990; Anderson et al., 1994).

Change data in the architecture of the parotid gland have scarcely been reported in the literature in obesity models. From the histological point of view, at adenomere level, a reduction in volume density (Vvad), surface density (Svad) and area density (NAad) were noted in both the MSG1 and MSG2 groups, which pointed to a reduction in the volume and surface of the adenomeres, which occupy within the gland, in addition to a decrease in the acinar cell number density (Nvac). These results are similar to those of Renzi et al., who reported hypotrophy of the adenomeres of the submandibular gland and a reduction in glandular mass after the induction of hyperphagia due to injury of the ventromedial nucleus of the hypothalamus, a lesion similar to that presented due to MSG consumption. By contrast, no changes were noted in the architecture of the submandibular gland in a model of genetically induced obesity (Zucker rats) (Renzi et al.) despite there being proinflammatory changes (Mozaffari et al.).

The total ducts decreased in both volume density and surface density in the groups exposed to MSG, indicating a reduction not only in striated ducts, but also in intercalated and excretory ducts. Although there are insufficient studies that link obesity to changes in the salivary glands, other obesity-related pathologies do show alterations in these glands (Lilliu et al., 2015). Additionally, decreases in the stereological parameters of the striated ducts in both experimental groups were observed, such as volume density (Vvstr) and surface density (Svstr) as a result of the MSG. This reduction is associated with concentration changes in salivary electrolytes in the MSG1 and MSG2 groups, where Na+ and Cl- were affected, electrolytes absorbed in the striated duct.

With respect to the functional parameters of the parotid gland, the experimental groups presented alterations in the amount and pH of saliva, as well as in the a-amylase concentration. The amount of saliva observed in the MSG1 and MSG2 groups was less, yielding statistically significant differences. Previously reported results (Modéer et al., 2010; de Campos et al., 2014; Choromanska et al., 2015) related reductions in salivary flow in obesity, associating this reduction with dental caries, thus strengthening even more the negative effect of obesity on oral health (Herrera et al., 1988; Leone & Oppenheim, 2001; Modéer et al., 2010). For their part, Sassaki et al. (2003) reported similar results in a MSG-induced obesity model. The pH decreased significantly in the groups exposed to MSG, demonstrating its effect on glandular function, results similar to those reported by Ain et al. (2016) in Indian children, where they noted the existing relation between the decrease in pH and the increase in BMI and decrease in salivary flow. The decrease in salivary pH could be due to the direct relation between salivary flow and amount of bicarbonate, because when there is less salivary flow, less bicarbonate is released, which reduces the pH. Matczuk et al. (2016) described the changes in the pH of the salivary glands as possibly leading to detrimental changes in their structure, impacting on their functions, and causing hyposalivation, similar to what was observed in our study. On the other hand, Pannunzio et al. (2010) did not observe any changes in the salivary pH in obese or overweight children compared to those of normal weight, the same result obtained with the parameter salivary flow.
α-amylase is an important component in the secretion of the parotid gland, secreted by the serous cells of the adenomere, with an important enzymatic function (Humphrey & Williamson, 2001; Rohleder & Nater, 2009). With respect to the α-amylase values, this enzyme increased in both groups exposed to MSG, thus in the animals in the MSG1 group, exposed to only 8 weeks, there were higher values, which decreased after 16 weeks, not reaching normality. This increase was reported previously by Sassaki et al. and Rodrigues et al. (2015) in obese animals, in MSG-induced obesity models and diets rich in fats, respectively. Although in our results there was a reduction in the number of acinar cells, the α-amylase secretion increased, which could be explained by a compensatory response by these cells. A possible explanation of the increase in active α-amylase could be due to the pH determined in the experimental groups, which are closer to the optimal activation pH of this enzyme, which are over pH 6 (Pedersen et al., 2018), being affected also in conditions of hypofunction of the salivary gland (Lynge Pedersen & Belström, 2019).

The glandular activity is intimately related to the morphological changes, explained partly by the proinflammatory effects induced by obesity/overweight in the salivary glands, produced mainly by the action of proinflammatory cytokines derived from adipocytes and macrophages present in the fatty tissue, which might negatively affect the function of the salivary glands (Modéer et al., 2011), in addition to the oxidative changes produced by MSG at glandular level, thus causing the development of oxidative stress (Beregova et al.; Hordiienko et al.).

CONCLUSION

Exposure to MSG caused morphofunctional alterations at parotid level, with a reduction in the volume of the gland being observed, accompanied by changes in the adenomere and striated ducts in the gland, involved in the production, secretion and modification of saliva, which was altered in flow, pH and in its components.

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