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Evaluation of body growth and myoenteric neurons of Wistar rats after neonatal treatment with monosodium glutamate

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ABSTRACT. This work aimed at evaluating how the neonatal treatment with monosodium glutamate reflects on body parameters and on myoenteric neurons of Wistar rats. Male rats were injected with monosodium glutamate during the first five postnatal days. Body growth was recorded until the age of 90 days, when the animals were killed. Fasting plasma glucose, caloric density and weight of organs were assayed. Gastric and duodenal whole-mounts stained with NADH diaphorase were observed for neuronal numbers and sizes. Growth, relative weight of organs and testicular caloric density of the injected rats were smaller than those of the controls, while their Lee index and relative fat content were greater. The number of duodenal neurons and the mean size of gastric neurons were smaller in the injected animals. These results are discussed in light of the endocrine, autonomic and behavioral changes stemming from the lesion of the hypothalamic arcuate nucleus by monosodium glutamate.

Key words: monosodium glutamate, body growth, calorimetry, myoenteric neurons.

Introduction

The hypothalamus is a region of the Central Nervous System (CNS) of extreme importance for the control of the vegetative and behavioral functions of mammals. Its actions are manifested at three major fronts: the control of most of the hormonal activity of the organism through connections with the pituitary, the modulation of the sympathetic and parasympathetic divisions of the Autonomic Nervous System (ANS), and the motor and emotional drive of behavior (Gray and Morley, 1986; Palkovits, 2003). Given the wide range of processes influenced by the hypothalamus, it is not surprising that it receives a variety of information on environmental and physiological conditions, relayed by neural and humonal signals. Also not surprising is the fact that the many hypothalamic nuclei have extensive projections to other areas of the CNS, both those phylogenetically more primitive and the more recent telencephalic areas (Chronwall, 1985).

The hypothalamus is intimately involved with the manifestation of reproductive, feeding, social and emotional behaviors of mammals. Some regions and nuclei of the hypothalamus are being investigated for the understanding of food ingestion...
behavior. For example, hypothalamic infusions of neuropeptide Y cause massive food ingestion. Neuropeptide Y also influences the release of metabolic hormones, fat metabolism, and body temperature. Neurons secreting neuropeptide Y are located at the hypothalamic arcuate (ARC) nucleus (Chronwall, 1985; Gray and Morley, 1986). The orexins form another group of neuropeptides whose involvement in feeding behavior has been recently emphasized. The orexin-secreting neurons have wide projections in the brain, and are in turn influenced by the ARC neurons, including those secreting neuropeptide Y. Leptin, a hormone produced by the adipose tissue, is one of the modulators of this pathway (Dawson et al., 1997; Sakurai, 1999).

The regulation of all visceral function is carried out by the ANS. Several hypothalamic nuclei, such as the paraventricular nucleus, the lateral hypothalamus and the ARC modulate, both directly and indirectly, the autonomic centers of the brain stem and spinal cord (Nijima et al., 1984; Chronwall, 1985; Gray and Morley, 1986; Kumar, 1999; Jiang et al., 2003; Palkovits, 2003).

The gastrointestinal system, responsible for the digestion and absorption of the food nutrients, is subject to autonomic modulation. In this instance the ANS is represented not only by sympathetic and parasympathetic fibers, extrinsic to the gastrointestinal tract, but also by an extensive intramural network of nerve fibers and neuronal cell bodies, the enteric nervous system, ENS (Gabella, 1979).

The enteric plexuses extend for the whole length of the digestive tract and have their cell bodies arranged in two sets of ganglia: the submucous plexus, primarily involved with the control of the secretory activity, and the myoenteric plexus, concerned with the control of the gastrointestinal motility. The ENS has a high structural complexity, which matches that of the CNS. The enteric neurons can control the gastrointestinal activity in a relatively independent manner, but are influenced and coordinated by sensory components of extramural projection and by the sympathetic and parasympathetic motor components (Gabella, 1979).

High doses of monosodium glutamate (MSG) applied to rodents during the neonatal period cause destruction of central neurons, especially in the ARC (Olney, 1969; Scallet and Olney, 1986; Hu et al., 1998; Goldsmith, 2000). When adults, these animals show, in addition to obesity, several endocrine changes (Bakke et al., 1978; Nemeroff et al., 1981; Dolnikoff et al., 1988; Gong et al., 1995; Macho et al., 2000; Franca et al., 2006) and autonomic alterations (Bray, 1984; Yoshida et al., 1984; Sartin et al., 1985; Leigh et al., 1992; Martins et al., 2004).

Despite the effects of the ARC lesion by MSG on many metabolic, physiologic and behavioral aspects being well documented in the literature, only recently this experimental model was employed to investigate its effects on the myoenteric neurons (Soares et al., 2006). Therefore, this work aimed at evaluating how the neonatal treatment with MSG affects several body parameters, such as ponderal and linear growth, weight of organs and adipose tissue, and whether it causes alterations in the number and size of the myoenteric neurons of the stomach and duodenum of Wistar rats.

Material and methods

Handling and treatment of the animals

Pregnant Wistar rats, supplied by the Central Animal House of the State University of Maringá, State of Paraná, were placed individually in cages at the animal house of the Department of Morphophysiological Sciences. One day after birth and for five consecutive days, the pups of the experimental group (group MSG) received cervical subcutaneous injections of MSG at the dose of 4 g kg⁻¹ body weight. The pups of the control group (group C) received injections of equimolar saline solution.

At 21 days of life the animals were separated from the mothers (weaning) and placed in collective cages. Body weight and naso-anal length were recorded weekly from birth to 90 days of age. During the whole experimental period the animals were under controlled conditions of light (light/dark cycles of 12/12 hrs) and temperature (22 ± 2°C), with free access to water and chow (Nuvital®, Curitiba, Brazil).

A 16-hrs fast was imposed to the animals of both groups before killing. This was made in the morning through cervical dislocation.

All the procedures of treatment, handling and killing of the animals were approved by the Ethics Commission on Animal Experimentation of the State University of Maringá (protocol CEEA 010/2004).

Determination of fasting plasma glucose

The blood of the rats was collected through puncture of the inferior vena cava just after killing. Fasting plasma glucose was determined through the enzymatic-colorimetric method of glucose oxidase (Bergmeyer and Bernt, 1974). All the samples were...
analyzed in duplicate, and the glucose level for the animal was established by the simple arithmetic mean of the two values obtained.

**Evaluation of obesity**

The body weight and the naso-anal length of the animals at the end of the experiment were used to calculate the Lee index \[\text{body weight}^{0.33} \times \frac{\text{g}}{\text{naso-anal length} \times \text{cm} \times 100}\] (Bernardis and Patterson, 1968). After opening of the abdominal cavity, the retroperitoneal and periepididymal fats were removed and weighted.

**Ponderal and calorimetric analysis of organs**

Liver, testes and the skeletal muscles of the hind limbs had their caloric content determined. Briefly, the samples were dried in a stove at 60ºC until constant weight, and ground to a fine and homogeneous powder. The energy content, or calorific density of the samples, was determined in a caloric bomb (Parr 1261).

**Analysis of the myoenteric neurons**

The stomach and duodenum were removed and subjected to the technique of the NADH diaphorase for staining of the enteric neurons. The segments were washed and filled with Krebs solution, pH 7.3, and kept distended by ligature of the endings. Next, they were washed twice in Krebs (10 min each), placed in 0.3% Triton X-100 solution for 5 min, again washed twice in Krebs (10 min each) and finally transferred to the incubation medium for 45 min (Gabella, 1969 and 1987; Furlan et al., 2002). This medium contains \(\beta\)-NADH and Nitro Blue Tetrazolium, the elements needed for the activity of the neuronal NADH diaphorase to result in the deposition of formazan and staining of the neurons. After incubation, the segments were opened and placed in 10% formalin solution for at least four days.

The stomach and duodenum were dissected to whole mounts through longitudinal opening at the mesenteric attachment and removal of the mucosa and submucosa. The smooth muscle layers, where the myoenteric neurons are located, were preserved. The whole mounts then were dehydrated, diaphanized and mounted in lamina for visualization at the optic microscope.

Neurons were counted in 40 microscopic fields of the glandular and aglandular portions of the stomach and of the mesenteric and antimesenteric regions of the duodenal circumference, under 40X objective. Neurons partially seen at the periphery of the field were counted in alternate fields.

Fifty neurons of each gastric portion (glandular and aglandular) and duodenal circumferential region (mesenteric and antimesenteric) of each whole mount were measured. The energy content of the neurons under 40X objective were transferred to a computer, and the area of the cell body profile was determined through an image analysis program (ImagePro Plus).

**Statistical analysis**

The data in each set are shown as mean ± standard deviation. The data sets obtained were statistically analyzed with Student’s t test at the significance level of 5%. The number of repetitions in each set is indicated in each case.

**Results**

Figure 1 shows the body weight evolution of the animals from groups C and MSG during 90 days. After weaning, the mean weight of group MSG was significantly lower than that of group C \(p<0.05\).

The naso-anal length of group MSG also remained significantly below that of group C during this period \(p<0.05, \text{Figure 2}\). The Lee index was significantly greater for group MSG \(337.2 \pm 14.45\) for group C, \(n=6\); and \(359.2 \pm 12.77\) for group MSG, \(n=6, p<0.05\), and so was the relative weight of the abdominal fats \(p<0.05, \text{Figure 3}\).

The right kidney, liver and testes were significantly smaller in group MSG, in terms of relative weight \(p<0.05, \text{Figure 4}\). The caloric density of the testes in group MSG was lower than in group C \(p<0.05\), while those of the liver and muscle were not different between the groups (Figure 5). Fasting plasma glucose did not differ significantly between the groups \(117.4 \pm 24.85 \text{mg dL}^{-1}\) for group C, \(n=6\), and \(99.80 \pm 32.35 \text{mg dL}^{-1}\) for group MSG, \(n=6\).

![Figure 1](image-url)
In both groups, the typical ganglionic arrangement of the mammalian myoenteric neurons was revealed by the staining of the neurons with NADH diaphorase. The neurons were distributed relatively evenly around the intestinal circumference, resulting in similar counts on the mesenteric and antimesenteric regions in each whole mount. Therefore, the data from both regions were pooled together and the analysis was made considering the total number of neurons in 80 microscopic fields per animal. The neuronal counts from the glandular and aglandular portions of the stomach were analyzed separately. Group MSG had a number of duodenal neurons significantly lower than group C (p<0.05), as shown in Figure 6. The number of neurons was not different between corresponding gastric portions of the stomach of groups C and MSG (p>0.05), as shown in Table 1. A great variation was observed on the neuronal counts from one whole mount to another of group MSG, especially for the stomach.

Table 1. Number of neurons in 40 microscopic fields of the glandular and aglandular portions of the stomach from group C (n=4) and MSG (n=4) at 90 days of age. *=p<0.05.

| Gastric portion | Group C | Group MSG |
|-----------------|---------|-----------|
| Glandular       | 931.3 ± 73.56 | 746.0 ± 257.50 |
| Aglandular      | 589.5 ± 41.11  | 635.8 ± 189.80  |

The mean sizes of the gastric neurons were smaller in group MSG, both at the glandular and the aglandular region (p<0.05), as can be seen in Figure 7. The neurons measured in each group were distributed in 10 size intervals (I-X), from 1 µm$^2$ to more than 901 µm$^2$, each interval spanning 100 µm$^2$.

Size interval distribution for the gastric neurons (Figure 7) showed that most of the neurons measured up to 300 µm$^2$ (intervals I to III). No neurons were found measuring more than 500 µm$^2$.
There was no difference on the mean size of the duodenal myoenteric neurons between group C (255.2 ± 176.6 µm², n=400) and group MSG (237.8 ± 183.4 µm², n=400). Most of the duodenal neurons measured in both groups showed sizes from 101 µm² to 400 µm² (intervals II, III and IV), a small number of neurons being greater than 801 µm² (intervals IX and X, Figure 9). Duodenal neurons from group MSG were more concentrated at size interval II.

Discussion

Several animals from group MSG died during the five-day period during which subcutaneous MSG injections were made and on the first few days thereafter. Saline injection did not result in death of any of the group C animals. The early death of the MSG-injected animals was also reported in another investigation (Bunyan et al., 1976) and is routinely observed in other MSG-treated rats of our laboratory. This is probably due to the injection being made at the cervical region, very close to the developing Central Nervous System, and to the natural fragility of the newborn rats.

In this study, the Lee index was greater in group MSG than in group C, much as the abdominal fat weight. The Lee index is regarded as an indirect indicator of obesity in MSG-treated rats (Bernardis and Patterson, 1968) and is often presented in studies of experimental obesity (Pizzi and Barnhart, 1976; Bakke et al., 1978; Scallet and Olney, 1986; Betran, 1992; Soares et al., 2006), although its accuracy and validity have been questioned by some authors (Cox et al., 1985; Stephens, 1980). On the other hand, the accumulation of adipose tissue in group MSG, given by the greater relative weight of the retroperitoneal and periepididymal fats, confirms that the treatment caused obesity. The greater efficiency in the storage of nutrients as fat was ascribed both to the autonomic impairment and the disturbance of the hypothalamic actions of leptin due to the ARC lesion caused by MSG (Bray, 1984; Dawson et al., 1997; Martins et al., 2004). Other changes which disturb glucose homeostasis, such as hyperinsulinemia, insulin resistance and imbalances of glucocorticoid activity (Sartin et al., 1985; Yamamoto et al., 1993; Hirata et al., 1997; Macho et al., 2000), must also be involved.

It is established that rodents neonatally treated with MSG become obese adults with reduced naso-anal length, body weight and relative weight of organs (Pizzi and Barnhart, 1976; Bakke et al., 1978; Hamaoka and Kusunoki, 1986; Nakai et al., 1986; Remke et al., 1988; Yamamoto et al., 1993). The results of the present investigation concerning these parameters are in accordance with the literature. It is probable that this dystrophy of growth of MSG-treated rats results from the significant decrease on the levels of growth hormone (GH) and insulin-like growth factor (IGF-I), as reported by some researchers (Nemeroff et al., 1977; Nakai et al., 1986; Miskowiak and Partyka, 1993; Yamamoto et al., 1993). Studies in primates and rats demonstrate that the cell bodies of the GH releasing hormone (GHRH)-secreting neurons are located in...
the ARC, with fibers projecting to the median eminence (Olney, 1969). The neonatal treatment with MSG results in selective destruction of these neurons, and this neuronal damage affects an area closely linked to the regulation of different functions, such as energy balance and functioning of the hypothalamus-pituitary and hypothalamus-adipose tissue axes (Bakke et al., 1978; Dolnikoff et al., 1988; Remke et al., 1988; Dawson et al., 1997). It can be suspected that the hormonal/metabolic alterations resulting from the neonatal treatment with MSG determined a change on the body protein/fat ratio, resulting in rats of smaller body weight and greater fat content.

The testes of the rats from group MSG had caloric density lower than those from group C. MSG animals have hypotrophy of gonads, prostate and pituitary (Pizzi and Barnhart, 1976; Pizzi et al., 1979; Hamaoka and Kusunoki, 1986; Miskowiak and Partyka, 1993). Low levels of gonadotrophic and gonadal hormones were also reported (Nemeroff et al., 1981; Gong et al., 1995; Franca et al., 2006). Therefore, the results of this study combine with those on the literature pointing to a reduced reproductive capacity of the MSG animals, which was confirmed in some investigations (Bakke et al., 1978; Nemeroff et al., 1981; Gong et al., 1995; Franca et al., 2006).

Significant differences were not observed for fasting plasma glucose between groups C and MSG, similar to some other descriptions (Bunyan et al., 1976; Hirata et al., 1997), but not to others, which report basal hyperglycemia in MSG-treated rats (Nakai et al., 1986; Macho et al., 2000). It is documented on the literature that MSG animals keep their normal basal glycemia due to a high hyperinsulinemia and that the tolerance to a glucose load is decreased (Scallet and Olney, 1986; Remke et al., 1988; Hirata et al., 1997).

The counts of the duodenal myoenteric neurons in 80 microscopic fields revealed a significant reduction in group MSG relative to group C, which probably represented a real decrease of the total number of NADH diaphorase-positive neurons of the duodenum. The duodenum of the animals from group MSG, similar to what happened to other organs, was probably smaller than that of the animals from group C, as was observed for the ileum (Soares et al., 2006), in such a way that, if there was not a reduction in the number of NADH diaphorase-reactive neurons the counts would have revealed values greater for the MSG than for the controls. In other words, the decreased dimensions of the duodenum on group MSG would have concentrated the NADH diaphorase positive neurons, yielding greater counts in this group. By the same token, probably more neurons were stained in the stomach of group MSG than of group C.

The reduction in the number of NADH diaphorase positive neurons does not unequivocally mean that duodenal myoenteric neurons were lost through necrosis or apoptosis. The technique of NADH diaphorase stains the myoenteric neurons based on the activity of this enzyme, so that for an incubation of 45 min, many neurons do not have enough NADH diaphorase activity to be stained and visualized. Thus, what can be ascertained is that, for the staining conditions employed here, the duodenal neurons from group MSG showed, collectively, lower NADH diaphorase activity than those from group C, and then fewer neurons were stained. In addition, as the NADH diaphorase activity of the neurons is related to the total metabolic level of these cells, it can be supposed that the duodenal neurons of the rats from group MSG showed lower metabolic activity than those from group C, as is characteristic of MSG obesity (Djazayery et al., 1979; Soares et al., 2006).

The MSG treatment exerted a slight yet not significant influence on the mean size of the myoenteric neurons of the duodenum, but did reduce the mean size of the gastric neurons from the glandular and aglandular portions. A significant reduction in the mean size of the NADH diaphorase positive myoenteric neurons was found in the ileum of MSG-treated rats, and this was ascribed to the reduced metabolism of the experimental model (Soares et al., 2006). Thus, while duodenal neurons responded to MSG treatment by decreasing their populational reactivity, gastric neurons responded by decreasing their size. Such a difference on the response profile of myoenteric neurons deserves further investigation, employing this and other staining techniques.

The neurons of the ENS are grouped in ganglia whose organization resembles that of the CNS, in which cell bodies and neuronal processes are surrounded by a ganglionic neuropil covered by connective tissue. The blood vessels of the enteric ganglia have properties similar to those of the cerebral hemato-encephalic barrier, limiting the access of macromolecules to the ganglion (Gershon and Bursztajn, 1978). In the CNS, the permeability of the hemato-encephalic barrier on the first postnatal days in rodents is one of the factors that allow MSG to reach the hypothalamus and exert its excitotoxic effects (Goldsmith, 2000). If the enteric hemato-ganglionic barrier have the same pattern of...
permeability as the hemato-encephalic barrier, that is, permeable during the first few days after birth, MSG itself could be the primary cause of the alterations observed on the enteric neurons, while the effects resulting from the ARC destruction by MSG (hormonal, metabolic and autonomic changes) would be secondary or late agents of the enteric modifications. It is not determined whether the doses of MSG employed would be sufficient to produce toxic levels of glutamate in regions of the body distant from the application site.

Conclusion

Neonatal Wistar rats treated with MSG show lower ponderal and linear development, obesity, reduced relative weight of organs and caloric density of the testes, altered number and size of myoenteric neurons. These changes probably result from the hormonal and autonomic dysfunctions due to hypothalamic ARC lesion by monosodium glutamate. As for the myoenteric neurons, a reduced number was found in the duodenum, while gastric enteric neurons had reduced sizes. It seems that other staining techniques, capable of staining the whole myoenteric neuronal population, would provide additional data for the understanding of the effects of MSG treatment on these cells.

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