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Monosodium glutamate, a food additive, induces depressive-like and anxiogenic-like behaviors in young Rats

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ABSTRACT

Monosodium glutamate (MSG) has been the target of research due to its toxicological effects.
Aims: We investigated the depressive- and anxiogenic-like behaviors in rats exposed to neonatal subcutaneous injection of MSG. The involvement of the serotonergic system, by measuring [^{3}H] serotonin (5-HT) uptake in cerebral cortices, and the hypothalamic pituitary adrenal (HPA) axis, by determining serum adrenocorticotropic hormone (ACTH) and corticosterone levels, was also examined.
Materials and methods: Male and female newborn Wistar rats were divided into control and MSG groups, which received, respectively, a daily subcutaneous injection of saline (0.9%) or MSG (4 g/kg/day) from the 1st to 5th postnatal day. The behavioral tests [spontaneous locomotor activity, contextual fear conditioning, and forced swimming test (FST)] were performed from the 60th to 64th postnatal day. MSG-treated animals showed alteration in the spontaneous locomotor activity, an increase in the number of fecal pellets and the number of animal's vocalizations and urine occurrence, and a decrease in the grooming time.
Key findings: The MSG exposure increased the immobility time in the FST and the freezing reaction in the contextual fear conditioning. Additionally, MSG treatment increased the [^{3}H]5-HT uptake in the cerebral cortices of rats and induced a deregulation of HPA axis function (by increasing serum ACTH and corticosterone levels).
Significance: In conclusion MSG-treated rats are more susceptible to develop anxiogenic- and depressive-like behaviors, which could be related to a dysfunction in the serotonergic system.
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Introduction

Monosodium glutamate (MSG) is one of a number of salt forms of glutamic acid, a non-essential amino acid, with unique flavor-enhancing qualities, that is widely used as a food additive. However, the safety of the use of MSG has raised concern. Recent research has demonstrated that MSG exposure produces metabolic changes, which can result in severe disturbances in animals and humans (Diniz et al., 2005; Insawang et al., 2012; Rotimi et al., 2012).

In animal models, subcutaneous neonatal MSG treatment induces neuroendocrine obesity through hypothalamic lesion (Nakayama et al., 2003; Xu et al., 2007) resulting in fat tissue accumulation, glucose intolerance, hyperinsulinemia, and insulin resistance (Balbo et al., 2007). It has been reported that obesity is not accompanied by hyperphagia (Martins et al., 2004). Moreover, MSG treatment induces neuronal damage by increasing lipid peroxidation (Babu et al., 1994) and degeneration in hippocampal CA1 pyramidal cells, which was associated with learning impairment (Ishikawa et al., 1997), hyperexcitability and motor behavioral alterations (Kiss et al., 2007; López-Pérez et al., 2010).

Depression and anxiety are serious diseases, characterized by imbalance of mood and emotions, beyond, abnormalities of limbic system structures, accompanied by reduction in monoaminergic signaling, with monoamine depletion, mainly of serotonin (5-hydroxytryptamine, 5-HT) (Meyer et al., 2006). Furthermore, depression is associated with a deregulation of the hypothalamic pituitary adrenal (HPA) axis, manifested by elevation in circulating glucocorticoids (Ge et al., 2013; Gold and Chrousos, 1999; Kostowski, 1985). The hyperactivity of the HPA axis in depression is thought to be particularly related to a deficiency in the inhibitory feedback mechanism by the endogenous hormones corticosterone and adrenocorticotropic hormone (ACTH), which are the most commonly altered hormones in depressive patients and animal models of depression (Odio and Brodish, 1990; Paskitti et al., 2000). In this context, Larsen et al. (1994) showed that plasma ACTH levels were lower in MSG-lesioned rats while corticosterone levels were elevated. In addition, the administration of MSG in rodents

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produces selective neuronal necrosis within the preoptic and arcuate *nuclei* of the hypothalamus as well as in the median eminence (Choi, 1994; Olney, 1969, 1971).

In this study we investigated the development of depression- and anxiety-related behaviors in young rats which were exposed to subcutaneous injection of MSG in the postnatal period. The involvement of the serotonergic system (by measuring the [^{3}H]5-HT uptake in rat cerebral cortices) and the contribution of HPA axis deregulation (by determining serum ACTH and corticosterone levels) were also examined.

Materials and methods

Animals

Male and female newborn Wistar rats were divided into two groups: I—MSG: rats received a subcutaneous injection of MSG (4 g/kg body weight per day) during the first 5 postnatal days, and II—control: rats received a subcutaneous injection of saline (0.9%) during the first 5 postnatal days (Balbo et al., 2000; Nardelli et al., 2011). Pups were weaned at the 21st day of life and had free access to standard rodent chow, under a 12:12 hour light/dark cycle, with lights on at 7:00 a.m. At the 60th day of life, the animals were submitted to behavioral tests (Fig. 1). The number of male and females was the same for all tests.

The animals were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources of the Federal University of Santa Maria, Brazil (# 050/2012). The procedures in this study were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals. All efforts were made to minimize animal suffering and to reduce the number of animals used in the experiments.

Drugs

L-Glutamic acid monosodium and other routine reagents were purchased from Sigma Chemical (St. Louis, MO, USA).

Behavioral tests

Spontaneous locomotor activity

The locomotor activity monitor (LAM) was used to investigate motor coordination. The locomotor activity monitor is a clear acrylic plastic box (45 × 45 × 45 cm) with a removable plastic lid perforated with holes for ventilation. The monitor contains photocell beams and detectors that are mounted on opposite walls (2 cm above the chamber floor). General locomotor activity and the rat position in the chamber are detected by breaks of the photocell beams, which are recorded by a computer. Animals were placed in the center of the apparatus and allowed to freely explore the arena. The number of crossings, rearings and fecal pellets, average velocity (mm/s), total distance traveled (mm), grooming time (s), the number of animal's vocalizations and urine occurrence were recorded for a 4 min period.

Forced swimming test (FST)

The FST was performed as described by Porsolt et al. (1979) and carried out over 2 days, i.e., a day for the pre-swimming session and a day for the test session. Briefly, in the pre-swimming session, rats were individually placed for 15 min in open cylinders (45 cm height × 20 cm diameter) containing 23 cm of filled water at 25 ± 1 °C. Twenty four hours later, rats underwent the test session. In the test session, rats were again placed in cylinders filled with water, and the duration of immobility was recorded during 6 min period. Each rat was recorded as immobile when floating motionless or making only those movements necessary to keep its head above water.

Contextual fear conditioning test

The contextual fear conditioning test was performed as described by Onishi and Xavier (Onishi and Xavier, 2010) with modifications. During the contextual training phase, each rat received ten footshocks (2.0 mA) with intervals of 20 s between the footshocks. Twenty-four hours after training, rats were individually transported to the experimental room and placed into the training chamber where they were maintained for 5 min. The time the animals spent exhibiting freezing during this session was measured. Freezing was considered as a "body immobility and the absence of vibrissae movement associated with sniffing" (Bouton and Bolles, 1980). At the end of the 5 min session the animals were removed from the chamber and returned to their home cages.

Ex vivo assays

After the behavioral tests, rats were sacrificed by decapitation and the cerebral cortices were quickly removed for the synaptosomal [^{3}H]5-HT uptake assay. Other groups of animals were anaesthetized with a single intraperitoneal injection of Equithesin (6 ml/kg), a mixture containing sodium pentobarbital (58 mg/kg), chloral hydrate (60 mg/kg), magnesium sulfate (127.2 mg/kg), propylene glycol (42.8%) and absolute ethanol (11.6%), for blood sample collection.

Synaptosomal [^{3}H]5-HT uptake

A synaptosomal suspension from cerebral cortices was obtained as previously described by Gray and Whittaker (1962). The [^{3}H]5-HT uptake into synaptosomes was carried out as previously reported by Rocha et al. (2007). Results were expressed as fentomoles of the [^{3}H]5-HT uptake per milligram of protein per minute.

Protein determination

Protein concentration of samples used for the synaptosomal [^{3}H]5-HT uptake was measured according to Bradford (1979), using bovine serum albumin (1 mg/ml) as the standard.

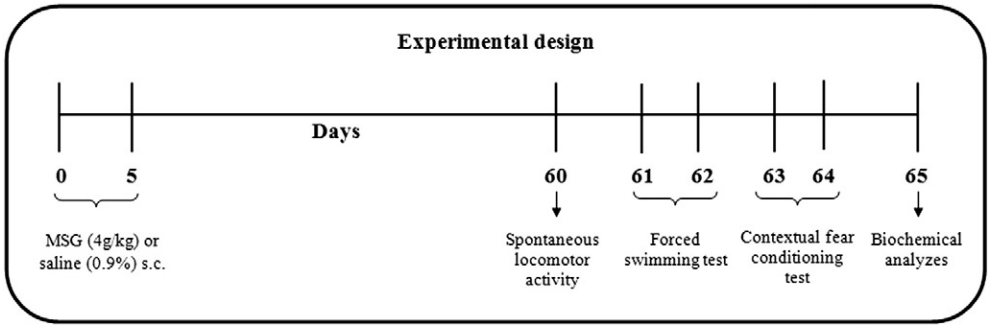

Fig. 1. Experimental design: rats received a subcutaneous (s.c.) injection of monosodium glutamate (MSG) or saline during the first five postnatal days. After the 60th day of life, the animals performed behavioral tests. 60th day: Spontaneous locomotor activity; 61st to 62nd: Forced swimming test (FST); 63rd to 64th: Contextual fear conditioning test. At the 65th day the animals were killed for biochemical analyses.

Determination of serum corticosterone and adrenocorticotropic (ACTH) hormone levels

Hormone levels in rat serum were carried out using a radioimmunoassay test kit (Coat-A-Count, Diagnostic Products Corporation, USA) according to the manufacturer's instructions.

Statistical analysis

The normality of data was analyzed using a D'Agostino and Pearson omnibus normality test. Data from behavioral tests, [^{3}H]5-HT uptake, serum ACTH and corticosterone levels were analyzed using unpaired Student's *t* test. Data from the total occurrence of vocalizations and urine in the LAM were analyzed by Fisher's exact test. Descriptive statistics data were expressed as the mean(s) ± SEM. Probability values less than 0.05 ($p < 0.05$) were considered as statistically significant. All analyses were performed using the GraphPad software (GraphPad software, San Diego, CA, USA).

Results

Subcutaneous injection of MSG increased the distance traveled by animals in the locomotor activity monitor

MSG-treated rats showed an increase in the total distance traveled ($p < 0.001$, Table 1). In contrast, the average velocity (mm/s) and the number of crossings and rearings were not altered in control and MSG groups (Table 1).

MSG-treated animals elicited an anxiogenic-like behavior in the contextual fear conditioning test and in the locomotor activity monitor

During the training phase of the contextual fear conditioning, both groups showed the same freezing time. The results obtained in the contextual fear conditioning test, twenty-four hours after training, showed that the time of freezing was increased in the MSG group when compared to the control one ($p < 0.001$, Fig. 2).

In addition, the number of fecal pellets ($p < 0.05$, Table 1) was increased in the MSG group, and also the number of animal's vocalizations ($p < 0.001$, Table 2) and urine occurrence ($p < 0.05$, Table 2). Furthermore, the time of grooming was markedly decreased in MSG-treated animals ($p < 0.05$, Table 1).

Subcutaneous injection of MSG induced a depressive-like behavior in the FST

The animals that received injections of MSG showed an increased time of immobility in the FST when compared to animals from the control group ($p < 0.001$, Fig. 3).

Table 1
Effects of MSG on behavioral parameters evaluated in the locomotor activity monitor.

Behavioral parameters	Control	MSG
Distance (mm)	4092.00 ± 316.30	6160.00 ± 457.70***
Number of crossing	663.20 ± 53.64	833.90 ± 78.80
Number of rearing	17.52 ± 1.60	22.40 ± 2.65
Velocity (mm/s)	21.78 ± 1.30	27.53 ± 1.80
Time of grooming (s)	27.27 ± 6.00	11.00 ± 2.00 *
Number of fecal pellets	1.50 ± 0.40	3.00 ± 0.50 *

Data are reported as means ± S.E.M. for fourteen animals per group. (*) Denotes $p < 0.05$; denotes (***) $p < 0.001$ compared to the control group (unpaired Student's *t* test).

Subcutaneous injection of MSG increased the [^{3}H]5-HT uptake in cerebral cortices

Animals exposed to MSG showed an increase in the [^{3}H]5-HT uptake in the cerebral cortex when compared to the control group ($p < 0.05$, Fig. 4).

Subcutaneous injection of MSG increased serum corticosterone and ACTH level

Rats from the MSG-treated group had an increase in corticosterone ($p < 0.05$) and ACTH ($p < 0.01$) levels (Table 3).

Discussion

The purpose of this study was to investigate the behavioral effects in young rats of subcutaneous injection of MSG in newborn rats. The results revealed that MSG exposure during the postnatal period increased the total distance traveled, number of fecal pellets, urine occurrence and number of animals' vocalization of young rats evaluated in the activity monitor. Furthermore, MSG-treated rats showed an increase in the time spent immobile during the FST and the freezing reaction in the contextual fear conditioning. In addition, we demonstrated an increase in the [^{3}H]5-HT uptake in cerebral cortices, and higher levels of ACTH and corticosterone in the serum of MSG-treated rats.

MSG, a non-essential amino acid, widely used in food industry, has been the target of research because of its highly toxic potential. A study from Kizer et al. (1977) demonstrated that the neurotoxic effect of MSG is more embracing to the neonatal period due to the immature blood–brain barrier; besides this effect seems to be dose-dependent. With agreement with Kizer et al. (1977) our data indicated that MSG crossed the blood–brain barrier given that this experimental protocol caused anxiogenic- and depressive-like behaviors in rats.

Results from the present study showed that MSG induced behavioral changes on the spontaneous locomotor activity of rats, demonstrated by an increase in the total distance traveled. In addition to the increase in locomotion, an anxiogenic-like behavior induced by MSG was demonstrated in this study. In fact, MSG-treated rats showed a decreased time of grooming during the spontaneous locomotor activity and an increase in the freezing time, suggesting an anxiogenic-like behavior. In support of this latter assumption rats treated with MSG showed an increase in vocalization, in the number of fecal pellets and in the urine occurrence, parameters that are related to anxiety-like behaviors. By contrast, Hlinak et al. (2005) demonstrated an anxiolytic-like behavior induced by MSG exposure to rats, when the behavioral paradigm was

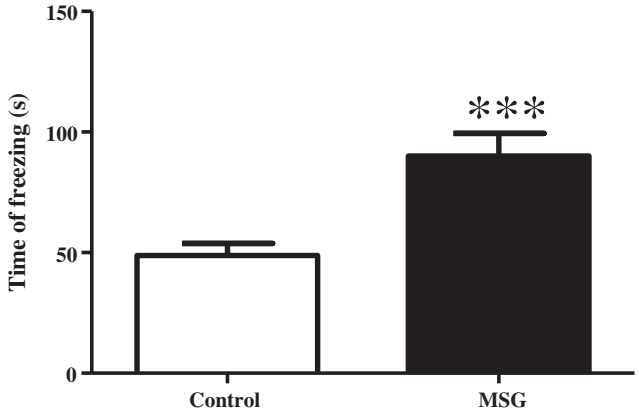

Fig. 2. Effect of MSG on the contextual fear conditioning test. Values are expressed as mean ± S.E.M. for 14 animals per group. (***) Denotes $p < 0.001$ compared to the control group (unpaired Student's *t* test).

Table 2
Effect of MSG on the number of animal's vocalizations and urine occurrence.

Group	Vocalization occurrence		Urine occurrence	
	YES	NO	YES	NO
Control	14/15	1/15	13/15	2/15
MSG	5/15	10/15***	6/15	9/15*

Data represent the mean ± S.E.M. for fourteen animals per group. (*) Denotes $p < 0.05$, and (***) denotes $p < 0.001$ compared to the control group (Fisher's exact test).

the elevated plus maze test. These authors found out that MSG-treated animals preferred the stay on the open arms, suggesting that the preference for the open arms may be related to a reduced anxiety, stress or frustration. It is important to note that the contradictory results between the Hlinak et al.'s (2005) study and ours could be due to some differences in the experimental protocol, such as the dose of MSG, the time of exposure and the age to which animals were challenged to behavioral tests.

Depression and anxiety are serious diseases in today's society, associated with significant levels of morbidity and mortality. Clinical studies indicate that the serotonergic system is strongly implicated in the etiology of these diseases, mostly accompanied with abnormalities in 5-HT neurotransmission (Hoyer et al., 2002; Wong and Licinio, 2001). In addition, selective 5-HT reuptake inhibitors (SSRIs) have been effective as antidepressants and anxiolytics for a long-term therapy (Argyropoulos et al., 2000; Zohar and Westenberg, 2000).

In the present study, the administration of MSG to neonatal rats induced both an anxiogenic-like behavior and a depressive-like behavior (characterized by the increase in the immobility time in the FST). Moreover, MSG-exposed animals demonstrated an increase in the [^{3}H]5-HT uptake in cerebral cortices. All together, these results suggest that MSG-exposed rats have a dysfunction in the serotonergic system which could be associated to the behavioral changes induced by MSG. Corroborating with the present results, Phelix and Hartle (1990) demonstrated that a subpopulation of serotonergic neurons in the area postrema of rats is more sensitive to the neurotoxicity of glutamate. This increased sensitivity of these neurons to MSG could partially explain the abnormalities in the serotonergic system observed in the present study.

Furthermore, depression is characterized by abnormalities of the limbic system accompanied by deregulation of the HPA axis (Gold and Chrousos, 1999; Kostowski, 1985; Spijker and Van Rossum, 2009). The hypothalamus is associated with the control of food intake, energy balance, and the autonomic nervous system (Macho et al., 2000). The administration of MSG in rodents produces selective neuronal necrosis

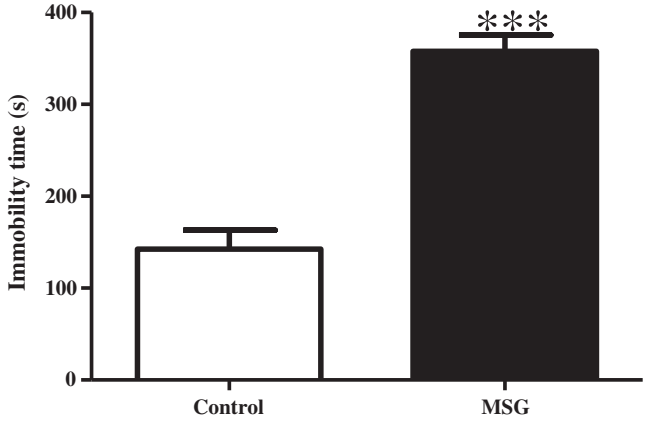

Fig. 3. Effect of MSG on the immobility time in the rat FST. Values are expressed as mean ± S.E.M. for 14 animals per group. (***) Denotes $p < 0.001$ compared to the control group (unpaired Student's *t* test).

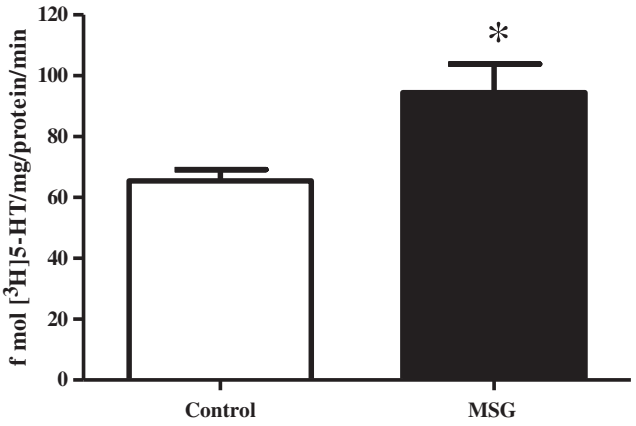

Fig. 4. Effect of MSG on the [^{3}H]5-HT uptake in the cerebral cortex. Values are expressed as mean ± S.E.M. for four animals per group. (*) Denotes $p < 0.05$ (unpaired Student's *t* test).

within the preoptic and arcuate *nuclei* of the hypothalamus as well as in median eminence (Choi, 1994; Olney, 1969, 1971).

Some authors have reported that functional changes of the HPA axis could be a trait phenomenon in mood disorders (Frodl and O'Keane, 2013; Phelix and Hartle, 1990). The activation of the HPA axis results in the release of hypothalamic corticotropin-releasing hormone (CRH), which in turn promotes anterior pituitary ACTH secretion, which triggers the synthesis and secretion of adrenal glucocorticoids (cortisol in humans, and corticosterone in rodents) into the circulatory system. Glucocorticoids released interact with their receptors in multiple target tissues including the HPA axis, where they are responsible for feedback inhibition on pituitary, hypothalamus, and extra-hypothalamic brain sites (Frodl and O'Keane, 2013; Antoni, 1993).

In line with that, the present study demonstrated an increase in serum corticosterone and ACTH levels in MSG-treated rats, which suggest a deregulation of the HPA axis in these animals. In other words we suggest that the elevated corticosterone levels are failing on inhibiting the secretion of CRH from the hypothalamus and ACTH from the pituitary, thereby up-regulating its own secretion. On the bases of the present findings one can hypothesize that the deregulation of the HPA axis is related to the behavioral changes induced by MSG in rats.

Although the extrapolation from studies with animals to humans should be done with caution, alterations in the HPA axis obtained in this study have been reported in depressive patients. In fact, increased secretion and reactivity of cortisol together with an altered feedback inhibition are the most widely observed HPA axis abnormalities in depressive patients (Zunszain et al., 2011). One possibility that cannot be ruled out is that the increase in serum corticosterone and ACTH levels in rats is a consequence of an excessive activation of the HPA axis caused by MSG.

Conclusion

Taking together, the results of the present study demonstrate that newborn rats exposed to subcutaneous injection of MSG are more susceptible to develop anxiogenic- and depressive-like behaviors. These behaviors were associated to the dysfunction in the serotonergic system,

Table 3
Effect of MSG on serum corticosterone and adrenocorticotropic hormone (ACTH) levels.

Hormone levels	Control	MSG
Corticosterone (ng/ml)	298.70 ± 47.69	458.70 ± 39.48 *
ACTH (pg/ml)	106.30 ± 15.49	163.70 ± 8.57 **

Values are expressed as mean ± S.E.M. for six animals per group. (*) Denotes $p < 0.05$, and (**) denotes $p < 0.01$ compared to the control group (unpaired Student's *t* test).

demonstrated by an increase in the [^{3}H]5-HT uptake in cerebral cortices, and deregulation in the HPA axis. Nevertheless, further studies are needed to better understand the toxicological mechanisms by which MSG induces behavioral alterations in rats.

Conflict of interest

The authors declare they have no conflicts of interest to disclose.

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