Veterinary Medical Journal –Giza (VMJG), Vol. 60 (2)B - , December 2014
http://www.vetmedjcu.com/
ISSN 1110-1423

Behavioral and Biochemical Effects of Monosodium Glutamate on Weaned Male Rats

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Abstract

The present study investigates the effect of long term treatment (0.06,0.3 and 0.6g/kg b. wt., orally) with monosodium glutamate (MSG) on open field test and some biochemical parameters such as cortisol, serotonin (5-HT) and monoamine oxidase activity (MAO) of post weaned albino rats for 3 months. Open field test showed a significant decrease in animal freezing and marked increase in horizontal movement expressed by number of crossed squares as well as vertical movement represented by number of rearing. In addition, MSG treated groups showed marked increase of cortisol level in serum, as well as serotonin (5-HT) level in frontal cortex. Moreover, significant decrement in monoamine oxidase (MAO) activity in frontal cortex had been observed. Results provide evidences that post weaned rats chronically exposed to monosodium glutamate which used widely as food additives showed decrease in anxiety and increase in hyperactivity.

Key words: Flavor enhancer, Food additives, Monosodium glutamate, Hyperactivity, Anxiety.

Introduction

Various environmental chemicals, industrial pollutants and food additives have been implicated as causing harmful effects, (Harsha and Anilakumar, 2013). Most known food additives are antioxidants, bulking agents, food coloring, flavors, flavor enhancers, glazing agents, stabilizers and sweeteners, (Khodjaeva et al., 2013).

The flavor enhancer monosodium glutamate (MSG), which is a sodium salt of glutamate, is one of the most flavor enhancer commonly used all over the world by millions of people in their food as it is a food additive in restaurants, hospitals, retirement homes and cafeterias. Moreover, it is found in a wide variety of canned and packaged food, (Jhon, 2006). Also in Egypt, Egyptians consume MSG in both ready and homemade food, almost daily, (Swelim, 2004). Monosodium glutamate improves taste stimulation and enhances appetite, (Vinodini et al., 2008).

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Over the past several decades, debate has been aroused about the safety of monosodium glutamates. Glutamate and its receptors are essential in the normal functioning of the brain and spinal cord, although excessive activation by glutamate is thought to contribute to neuronal damage in many neurological disorders ranging from hypoxic–ischemic and traumatic brain injuries to chronic neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease, (Pelligrini-Giampetro et al, 1997 and Platt, 2007).

Monosodium glutamate in high doses produced neuroendocrine abnormalities, neurodegeneration, neurotoxicity and oxidative damage in different organs in rodents (Harsha and Anilakumar, 2013). Moreover, the hormonal alterations caused by MSG treatment affect the physical state and behavior, especially in neonates' rodents who have an immature blood-brain barrier, (Larsen et al., 1994). The incidence and severity of the lesions done by MSG varied according to the dose level and the age of the animals, (Monno et al., 1995).

Most of the animal studies dealt with high doses of MSG (third of lethal dose) and administered to rodents either subcutaneous (s.c.), (Bodnar et al., 2001, Olvera-Cortes et al., 2005, Lopez-Perez et al., 2005 and Kiss et al., 2007) or intraperitoneal (i.p.), (Kuznetsova, et al. 2007, Harsha and Anilakumar, 2013, Shivasharan et al., 2013, and Swamy et al., 2013) but this can't give us a clear picture of the effect of MSG in our diet. Moreover, previous studies mainly inject MSG in neonates, (Olvera-Cortes et al., 2005, Lopez-Perez et al., 2005, Kiss et al., 2007, Kuznetsova et al., 2007) or adult animals, (Eweka and Om'Iniabohs, 2008, Shivasharan et al., 2013 and Swamy et al., 2013).

Therefore, the objective of the present study was to evaluate the possible anxiogenic or the anxiolytic effect of MSG on weaned. Anxiety like behavior and hyperactivity were measured and the biochemical profile was monitored.

Materials and methods

Animals and Locations

Eighty weanling Wistar male rats, weighing approximately 55-65g were obtained from the unit of laboratory animals at National Organization of Drug Control and Research NODCAR and used in the study. They were housed in standard plastic cages with stainless steel wire lids, bedded with wood shavings. Animals were maintained on a 12- h light/dark cycle at a constant room temperature of 20-22 and 60 % relative humidity. Feed and water were offered ad libitum throughout the course of the present study. All efforts were made to minimize the numbers of animals and their suffering in this study

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following the guidelines released by Cairo University Policy on Animal Care and Use.

Administration of Monosodium Glutamate

All animals were distributed randomly into four groups having 20 animals each. The route chosen in this study for exposure was oral gavage to mimic human exposure. Animals were administered our treatments, throughout the study till its completion, for 12 weeks as follows:

Group (1) control (c), n=20 weanling male rats were administered physiological saline.

Group (2), (3) and (4) received MSG orally at 0.06, 0.3 and 0.6 mg/g body weight, respectively, (Oneyma et al., 2006 and Eweka and Om'Iniabohs, 2008) dissolved in physiological saline, (Mohamed, 2012).

Behavioral Measurements

Anxiety like Behavior and Locomotion

The open field test provides simultaneous measures of locomotion, and anxiety like behavior, (Kelly, 1993 and Millan, 2003). The open field was a square wooden arena measured (90 x 90 x 25cm).The wood of the apparatus is covered with a plastic laminate (formica), which prevents absorption of fluids (urine of rats). The floor was divided by black lines into 36 small squares (15 x 15cm). The open field maze was cleaned between each rat using 70% ethyl alcohol to avoid odor cues. The rats were carried to the test room in their home cages and tested once at a time for 3 minutes each. Rats were handled by the base of their tails at all times. Rats were taken from their home cages and placed randomly into one of the four corners of the open field facing the center. The behavioral scores measured in this experiment included total numbers of line crossings (number of squares), rearing against the wall, as well as the time spent freezing (no movement) was quantified. (Table 1)

Biochemical Measurements

Blood and Tissue Sampling

On completion of all behavioral assessments, blood samples were collected from retro orbital venous plexus and drown by vein puncture into serum separation tubes (Schemer, 1967). The blood was allowed to clot at room temperature for 30 minutes. Serum was then separated by centrifugation at 3000 revolution per minute (rpm) for 10 minutes at 4°C using cooling centrifuge. The separated serum was

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collected and stored at -20°C for determination of cortisol. Thereafter, rats were sacrificed by decapitation and the brain was immediately removed, and the fore brain was dissected, weighed and kept at -20°C until determination of serotonin content and monoamine oxidase activity.

Determination of blood cortisol

Cortisol was determined in serum sample using commercial ELISA kits (Immunospec. Corp. USA) according to the method of Foster and Dunn (1974).

Estimation of amine levels:

Each tissue sample was weighed and hemoginized in 3 ml ice-cold acidified n-butanol using glass homogenizer. Homogenization of tissue and recovery of serotonin from tissue homogenates has been described previously by Maickel et al. (1968). The serotonin content was determined in frontal cortex according to the fluorometric method of Ciarlone (1978).

Determination of monoamine oxidase (MAO)

Tissue samples where weighed and homogenized in 0.2M phosphate buffer, pH 7.4 (2%w/v). The fluorescent product 4-hydroxyquinolone (4-HQ) was measured in a spectrofluorometer at 315 nm (excitation) 380 nm (emission) according to a modification of the fluorometric method of Krajl (1965).

Statistical analysis

Statistical analyses were performed by using SPSS 18 for Windows (SPSS Inc., Chicago, USA). Data are presented as means ± S.E. Homogeneity of the data was confirmed before ANOVA, differences among the experimental groups were assessed by one-way ANOVA followed by Tukey or Tamhane's T2 and differences were considered statistically significant at probability level less than 0.05 for all tests.

Results

Anxiety like Behavior and Locomotion

The effect of MSG treatment on parameters of open field test was illustrated in (Table 1). MSG-treated rats increased significantly the mean covered distance in the open field test when compared with the control group ($p < 0.05$) as well as a significant increase of rearing ($p < 0.05$). On the other hand, significant decreased time spent freezing took place ($p < 0.05$).

Veterinary Medical Journal –Giza (VMJG), Vol. 60 (2)B- , December 2014
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Table1: Effect of MSG administration on open field test parameters.

Group Parameter	Control group	(Low-MSG) Group (0.06mg/g)	(Medium -MSG) group (0.3mg/g)	(High-MSG) Group (0.6mg/g)
Freezing time(s)	7.3±1.4	2.4±0.7*	1.4±0.6*	1.8±0.6*
Total no. of squares crossed	14.5±9.4	34.0±19.2*	39.1±14.7*	32±15.7*
No. of rears	2.3±1.3	3.7±3.5*	5.6±4.9*	4.07±2.1*

(*) values (mean ± S.E.) within row differ significantly ($p < 0.05$).

Blood cortisol:

Cortisol level was significantaly increased in rats treated with low and medium doses of MSG ($p < 0.05$ - Table 2), when compared to those in control group. Nonsignificant increase was observed in high treated group (0.6 mg/g).

Serotonin

In the present study, serotonin was markedly increased in frontal cortex in all MSG treated groups compared to control one ($p < 0.05$ - Table 2). This increasing was not significant at medium MSG group.

Monoamine oxidase

Monoamine oxidase activity was significantly decreased in frontal cortex in monosodium glutamate treated groups ($p < 0.05$ - Table 2), despite this decrement was non-significant at low-MSG group.

Table 2: Effect of MSG administration on some biochemical parameters in rats.

Parameter \ Group	Control group	(Low-MSG) Group (0.06mg/g)	(Medium -MSG) group (0.3mg/g)	(High-MSG) Group (0.6mg/g)
Bl. cortisol (µg/dl)	1.36±0.12	2.35±0.23*	2.91±0.22*	1.67±0.12
Serotonin level (µg/g tissue) in frontal cortex	0.099±0.01	0.132±0.007*	0.108±0.009	0.129±0.007*
Monoamine oxidase activity (µM 4-HQ/hr/g tissue) in frontal cortex	9.08±0.40	8.48±0.27	7.37±0.46*	7.53±.070*

(*) values (mean ± S.E.) within row differ significantly ($p < 0.05$).

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Mechanisms are similar in rodents and humans, thus a valid reliable model of rodents would be of a great utility for studying different behaviors (Agmo et al., 2004).

Monosodium glutamate (MSG) has been used widely as a food additive but when it is administered to newborn rodents (intraperitoneally or subcutaneously); it produces excitotoxic damage to different brain regions, along with behavioral and metabolic changes, (Gonzalez-Burgos et al., 2001). These excitotoxic effects appear to be mediated by different glutamatergic receptors over-stimulation and including several physiological abnormalities, (Rodriguez et al., 2000 and Cull-Candy et al. 2001) such as neuroendocrine deficiencies involving metabolic, reproductive and growth disturbances (Dawson and Annau, 1983).

Hence, young animals are more susceptible than adults to the MSG toxic effect, (Olney 1978 and 1980) possibly because the amino acid intake mechanisms are not yet completely functional, or because the blood-brain barrier has not been completely established, or both reasons combined in a newborn animal, (Ortuno-Sahagun et al., 1997).

The current study was designated to evaluate the effects of monosodium glutamate in weanling male rats on anxiety like behavior and hyperactivity as well as biochemical changes. Glutamate within the brain and spinal cord has more functions than being a simple excitatory neurotransmitter, as it is important in the pathogenesis of anxiety disorders such as attention deficit hyperactivity disorders (ADHD), Alzheimer's disease, Parkinson's disease and Huntington's disease, (Onaolapo et al., 2012).

In open field test, treated rats showed a significant decrease in freezing time and a markedly increase in vertical and horizontal movement. These results may indicate a decrease in anxiety and increase in hyperactivity. Locomotor activity has been reported both to be increased, (Araujo and Mayer, 1973, Katz, 1983, Klingberg et al., 1987, Saari et al., 1990 and Dubovicky et al., 1997) or decreased, (Pizzi and Barnhart, 1976, Poon and Cameron, 1978, Iwata et al., 1979, Seress 1982 and Hlinak et al., 2005) following neonatal MSG treatment. Reasons for this discrepancy may include differences in the apparatus employed, route of administration and age of animals treated and/or length of time for which observations were made, (Ali et al., 2000). Hyperactivity is a result from decreased anxiety during situations that should normally be threatening. Hyperactive rats showed an overall behavioral pattern consistent with reduced anxiety on open field test that measure anxiety induced by anxiogenic factors for rodents, such as open space. The association of food additives with hyperactivity is a popularly accepted notion. The causation of this condition by food additives is somewhat controversial, although a number of controlled clinical trials that have eliminated food colorings, preservatives, and flavor enhancers from the diets of hyperactive children have shown an improvement in behavior (Lau et al., 2005).

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Veterinary Medical Journal –Giza (VMJG), Vol. 60 (2)B- , December 2014
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Discussion

Animals having predictive validity to human responses or physiological processes are good models, (Giraldi et al., 2004). The basic neural and behavioral

The biochemical assessment in this study indicated elevated cortisol level in monosodium glutamate treated rats. Several reports showed a persistent elevated blood corticosterone levels in adult animals neonatally treated with monosodium glutamate, (Dolnicoff et al., 1988, Magariños et al., 1988, Macho et al., 1999 and Kuznetsova et al., 2007).

Cortisol and corticosterone are glucocorticoids secreted from adrenal glands and controlled by adrenocorticotropic hormone (ACTH). They present in detectable or similar amounts in plasma. The reasons underlying the presence of two different glucocorticoids hormones in the plasma of some species (e.g. rat and mice) are not understood at present. It is widely assumed that cortisol and corticosterone share the same physiological roles, (Vera et al., 2012).

Macho et al., (1999) suggested that elevated corticosterone level in MSG treated rats is due to elevated corticosterone production in adrenals and lower degradation rate in liver. This modification of the adrenocortical system is expected to produce changes in the animals' behavior (Kuznetsova et al., 2007). Kuznetsova et al., (2007) agreed with the present study that an increase of blood corticosterone was accompanied by a decrement in levels of anxiety as the time spent in the open arms of the maze was greater after administration of sodium glutamate than in intact mice, supporting the notion that there was a reduction in the level of anxiety accompanied by high level of corticosterone.

Concerning the effect of MSG on frontal cortex, brain region involved in the regulation of mood and performance, (Chimakurthy and Talasila, 2010), serotonin (5-HT) was markedly increased in frontal cortex in our study. However, previous researches did not fit with the elevation of 5-HT in the frontal cortex of MSG treated groups, (Nakagawa et al., 2000, Waggas et al., 2009 and Harsha and Anilakumar, 2013). These differences between subject areas may be ascribable to the disputes between the methodologies such as species and developmental level.

Serotonin level is the principle monoamine involved in the pathogenesis of many anxiety disorders where low levels of 5-HT is associated with anxiety and the possible mechanism involved in the anxiolytic-like effect of many substances can be attributed to increases in the 5-HT level, (Chimakurthy and Talasila, 2010). Accordingly, it could be concluded that the increment of 5-HT in frontal cortex in MSG treated rats observed in our study may explain the decrease of anxiety.

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In the present study, monoamine oxidase activity (MAO), a mitochondrial enzyme responsible for the oxidative deamination of a variety of biogenic amines, was significantly decreased in frontal cortex. The increment of 5-HT level following long-term treatment with MSG in the developing rats may be due to a decrement in MAO as represented from the present study.

Conclusion:

In conclusion, the current study confirms that the flavor enhancer monosodium glutamate even at low doses causes behavioral implications as well as biochemical disturbances. Based on the existing study, consumption of monosodium glutamate at childhood leads to hyperactivity. Furthermore, disturbances in serotonin and elevation of blood corticosterone are an impact of monosodium glutamate intake. Accordingly, care should be taken especially in hyperactive children to decrease the consumption of food that contains monosodium glutamate. Further researches should be completed to estimate the effect of monosodium glutamate with other food additives.

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تأثير أحادي جلوتاميت الصوديوم علي التغيرات السلوكية و البيوكيميائية في الفئران البيضاء حديثي الفطام

الملخص

هذه الدراسة تم تصميمها لدراسة تأثير ملح جلوتاميت أحادي الصوديوم (الجرعات الآتيه مج/جم)علي سلوك الفئران البيضاء وكذلك علي بعض القياسات الكيميائية .أوضحت ٠.٠٠ ، ٠.٠٠ ، ٠.٠٠ ، ٠.٠٠ النتائج أن ملح جلوتاميت أحادي الصودي يسبب النشاط الزائد المصاحب لنقص القلق عند الفئران من خلال زيادة نسبة الكورتيزول في الدم و زيادة نسبة السيروتونين في المخ المصاحب لنقص انزيم الأمين أوكسيديز. تم اجراء هذه الدراسة في بيت الحيوان الخاص بشعبة تقييم الهرمونات في الهيئة القومية . من المعلوم أن الطعام لا يقتصر فقط علي ٣.٠٠ حتي أكتوبر ٣.٠٠ للرقابة و البحوث الدوائية من يناير الامداد بالقيمه الغذائية انما أيضا هو نوع من المتعه .لذلك فقد استخدمت مضافات الأغذية منذ سنين عديده لتحسين الطعم و اللون واطالة فترة الصلاحية .ان محسنات الطعم هامه جدا في صناعة الأغذية وأحدى هذه المحسنات هو أحادي جلوتاميت الصوديوم. اعتمدت أغلب الأبحاث السابقة علي استخدام جلوتاميت أحادي الصوديوم في إحداث السمية العصبية عن طريق حقن جرعات عالية منه في حديثي الولاده غالبا . بينما يوجد عدد محدود من الأوراق البحثية التي درست تأثير أحادي جلوتاميت الصوديوم علي فترة البلوغ بجرعه تضاهي تناول الأنسان وتضاهي أيضا العمر الذي يتعرض فيه الانسان بصوره كبيره لمضافات الأغذيه . لذا كان الهدف من هذه الرسالة هو دراسة تأثير تناول أحادي جلوتاميت الصوديوم لمده طويلة علي ذكورالجرذان حديثي الفطام من حيث : - سلوكيات النشاط الزائد و القلق ٠ . - مستوي الكورتيزول في الدم ٣ . - مستوي السيروتونين ٠ - نشاط أنزيم احادي الامين اوكسيديز ٤ من ذكور الجرذان الغير بالغة في هذه الدراسه .ولقد تم الحصول علي هذه ٠. خدم عدد است الجرذان من وحدة حيوانات التجارب التابعه للهيئة القومية للرقابة والبحوث الدوائية. تم توزيع الجرذان : جرذ .تم تقسيم المجاميع كالآتي ٣. علي اربع مجموعات بحيث تحتوي كل مجموعه علي

المجموعة الأولي :هي المجموعه الضابطه و التي يتم تجريع الفئران محلول ملحي فقط.) مج/جم ٠.٠(

المجموعة الثانية :يتم اعطاء جرعه منخفضه من أحادي جلوتاميت الصوديوم . أسبوع ٠٣عن طريق التجريع لمدة مج/جم)عن ٠.٠(المجموعة الثالثة :يتم اعطاء جرعه متوسطة من أحادي جلوتاميت الصوديوم . أسبوع ٠٣طريق التجريع لمدة) مج/جم ٠.٠(المجموعة الرابعة :يتم اعطاء جرعه منخفضه من أحادي جلوتاميت الصوديوم . أسبوع ٠٣عن طريق التجريع لمدة وقد اوضحت النتائج الآتي: - ارتفاع سلوك النشاط الزائد المصاحب لانخفاض التوتر للفئران الحاصله علي أحادي ٠ جلوتاميت الصوديوم. - ارتفاع مستوي السيروتونين في المخ المصاحب لانخفاض نشاط انزيم احادي الامين ٣ اوكسيديز. . - ارتفاع معدل