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Assessment of Morphological Changes and Antioxidant Status in Neocerebellar Cortical Layers of Adult Wistar Rats Following Monosodium Glutamate Exposure

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Abstract: Some effects of monosodium glutamate that is commonly used as food additive and flavor enhancer were evaluated on histological, and biochemical parameters on neocerebellar cortical structures in adult Wistar rats following monosodium glutamate induced toxicity. Forty eight adult male Wistar rats weighing between 70-130g (8-10 weeks old) were randomly separated into four groups, each containing twelve rats. The rats in group A were regarded as the controls and they received only distilled water during the treatment period. The rats in group B, C and D were MSG-treated rats. The Wistar rats in group B, C and D received respectively 2g/kg, 4/kg and 6g/kg body weight of MSG orally once duty for 28 consecutive days. The rats were euthanized on 29th day of the treatment. The cerebellum were carefully dissected out before removing halves of the neocerebellar cortical tissues for the preparation of the homogenate samples for assessment of oxidant and antioxidant parameters, Lipid peroxidation(LPO); malondialdehyde (MDA), super oxide dismutase (SOD), catalase (CAT) glutathione (GSH) and nitric oxide (NO). The remaining neocerebellar and neocerebral cortical samples were fixed immediately in 10% buffered formal saline for routine histological procedures for evaluation by light microscopy. The results from tissue analysis on oxidant and antioxidant parameters indicated a dose-dependent, significant increased ($P<0.05$) in lipid peroxidation (LPO) and nitric oxide (NO) in the neocerebellar cortical tissues in MSG-treated rats compared with controls. Conversely, the cortical SOD, CAT and GSH decreased significantly ($P<0.05$) in MSG-treated rats compared with controls. This histological findings from the MSG – treated rats demonstrated some atrophic and neurodegenerative changes in the cortical neurons. Some neocerebellar Purkinje cells appeared shrunken, pyknotic and degenerative coupled with vacuolization of the neuropile or stroma of the cortex. Conversely, the neocortical sections from the control rats appeared normal as the cortical neurons showed regular outlines. This study concluded that prolonged exposure to MSG may result in neocerebellar cortical damage which might be due to oxidative stress induced by excitotoxicity of MSG and consequently the cerebellar functions might be compromised.

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INTRODUCTION

Monosodium glutamate (MSG) also called Umani has been used as a flavor enhancer for 100 years in household food preparation and commercially processed foods (Ka et al, 2011). It was believed that MSG was only used in Asian cuisine for decades, today MSG has become one of the world's most widely used food additives. It exists in most processed foods but may be hidden on ingredient labels and listed under other names (Erb and Erb, 2003; Ito, 2008). (Research findings have shown that large variations exist in MSG consumption within and across populations.

About 25% of the human population is reported to be sensitive to MSG (Keir et al, 1979). MSG still remains a widely and commonly used flavor enhancer (Onyema et al, 2012). The category of people that reacts adversely to MSG does so even at doses recommended in food (Schaumburg et al, 1969). Some recent studies have reported some metabolically toxic effect of MSG with a number of the reports indicating the induction of oxidative stress in different tissues of experimental animals after administration of chronic doses of MSG (Shingh et al, 2003;Diniz et al, 2004; Farombi and Onyema, 2006; Onyema, 2006).

The liver plays an important role in the metabolism of glutamate, the conversion of some glutamate to lactate occurs in the liver, while the kidney is involved in its elimination although some MSG is metabolized by conversion into alanine in the intestinal mucosa (Garattiini, 2000). Diary dietary consumption of glutamate varies from one race to another, however, daily oral consumption ranges from 0.5mg/kg among Americans and over 3g/kg in Taiwanese (He et al, 2008 and Shi et al, 2010).

MSG is widely used flavor enhancing food additive that may be present in packaged foods without appearing on the label (Ismail, 2012). This flavor enhancer was isolated in the laboratory not very long ago and identified as MSG. at a later stage, this flavor gained great popularity worldwide. It has been in use particularly since then in restaurants particularly soups and mixed in noodles , packaged food industries (instant meals) and household kitchens (Ismail, 2002). Modern commercial MSG is produced by fermentation of starch, sugar, beet sugarcane or molasses (Walker and Lupien, 2000).

Glutamate might trigger neuro inflammation through its effect on immune cells (Ismail, 2012).

However, the adverse effects of MSG in humans appear to manifest in MSG – sensitive individuals suggesting that some people may have an MSG intolerance that causes MSG symptom complex with some symptoms such as headaches, or migraine in some individuals (Ismail, 2012). MSG gives rise to a characteristic taste called Umani (Yamaguchi and Ninomiya, 1998).

Despite the normal physiological function of glutamate as excitatory neurotransmitter, exogenous administration of high doses of glutamate or of MSG and other agonists induces neurotoxicity in several brain regions (Alfonso et al, 2009).

Monosodium glutamate otherwise known as Aji-no-moto is the sodium salt of glutamate acids. glutamate is one of the most common amino acids in nature and is the main component of many proteins and peptides of most tissue (Inuwa et al, 2011). Monosodium glutamate contains 78% glutamate acid, 22% sodium and water (Adrienne, 1999). Glutamate is also produced in the body and plays an important/essential role in human metabolism (Inuwa et al, 2011).

Findings have shown that most communities and individuals in Nigeria often use MSG as a bleaching agent for the removal of stains from clothes and other textile materials and this excellent bleaching property of MSG could be harmful to tissues and organs of the body when ingested as a flavor enhancer in food (Okoneta, 2013).

There is accumulating evidence that is excellent bleaching properties could be injurious or harmful to the cells and tissues of the body or worse still inducing terminal diseases in consumers when ingested as a flavour enhancer in food (Inuwa, 2011). However, despite its possible adverse consumer's response to MSG, reputable international organizations and nutritionists have continued to approve its usage and reiterated that MSG has no adverse reactions in humans (Okwuraine, 1992).

The food and Drug administration (FDA) of the United State had reported that monosodium glutamate is safe and that it should be maintained on the "General recognized as safe (GRAS) – list of foods (Inuwa et al, 2011). MSG is thus reportedly permitted as a safe food additive that needs the specific average daily intake or an upper limit intake requirement. Similarly, National Agency for Food and Drug Administration control (NAFDAC) has also reported that MSG is not injurious to health (Rogers and Blundell, 1990). The US Food and Drug Administration (FAA) has further admitted that processed free glutamic acid found in reaction flavors which are produced from a combinations of specific amino acid reducing sugars, animals or vegetable fats, or oils and optional ingredients including hydrolyzed vegetable protein are carcinogenic (Food Chemical News, 1993). Glutamate and monosodium glutamate are salts of glutamic acid technically (Otney, 1989). The cerebellum is a region of the brain that performs a number of important motor and cognitive functions, including motor learning, time perception and precise movement (Salman, 2002, Matemura et al, 2004). The cortex has become the focus of particularly intense research because it is presumed to be responsible for planning learning movement.

MATERIALS AND METHODS

Animal Care

48 male Wistar rats between 8 and 10 weeks old were used for the study. The rats were maintained in the Departmental Animal Holdings. The rats were housed in standard animal cages, fed with standard rat chow purchased from and drinking water was given to the Wistar rats *ad libitum*. The rats were maintained under standard laboratory conditions. The Wistar rats were given adequate care in accordance with the principles of laboratory and animal care (Institute of Laboratory Animal Resources 1996). All the Wistar rats were subjected to 2 weeks acclimatization period prior to treatment before they were carefully screened and confirmed to be healthy during the acclimatization period. Body weights of the rats were monitored during this period using a sensitive weighing balance.

Test materials

Ajinomoto which is one of the trade names of the concentrated forms of Monosodium Glutamate was procured from Open market, Ogbomoso, Nigeria. The test material (MSG) was stored and protected from direct sunlight until the time of administration which was done orally using a syringe and canulla.

Chemicals

Kits and all chemicals used for assessment of oxidative enzymes parameters (MDA, SOD, CAT, GSH, NO) were of analytical grades and purchased from Sigma Chemical Co. St. Louis, Mo, USA

Experimental Design and Grouping

The 48 male Wistar rats weighing between 90g and 120g were randomized into four main groups, each containing 12 rats as follows:

Group A (n = 12) served as the normal control group, they received only distilled water and the Wistar rats in this group remained in their home cages throughout the experimental period.

Group B MSG- treated group (n = 12) was treated orally with aqueous solution of MSG (2g/kg) of body weight/day for 28 days).

Group C (n = 12) treated with 4g/kg MSG for 28 days.

Group D (n = 12) treated with 6g/kg MSG for 28 days.

The selection of the above doses was based on the previous reports by Sareesh *et al* (2010), Vinodini *et al* (2010) and Eweka *et al* (2007)

Monosodium glutamate was obtained from the open market in Ogbomoso, Oyo state.

Animal Sacrifice and Collection of Brain Samples

The Wistar rats were euthanized on 29th day of the treatment the brain of each rat was immediately removed by dissection following the method of Abeer, (2009 before fixing in 10% buffered formalin in accordance with previous investigators (Zhang *et al*., 2012; Mai,2013) for light microscopy using Hand E as described by Wilson and Gamble(2002)

Lipid Peroxidation (LPO) assay: Neocerebral and neocerebellar cortical malondialdyde (MDA) level was estimated in the respective homogenate samples obtained from each group by employing the procedure of Vashney and Kale (1990).

Superoxide Dismutase (SOD) assay: SOD activity was estimated using the method of Mishra and Fridovich (1972).

Catalase Assay: the catalase activity of each cortical homogenate sample was determined according to the method of Aebi (1983)

Glutathione Assay: The reduced glutathione (GSH) content of the neocerebellar and neocerebral samples of homogenate prepared was determined using the method described by Jollow et al (1974).

Determinatiom of Nitric Oxide: Nitric oxide was determined through the determination of nitrate and nitrite by the method of J.R Thayor and R.O Huffaker (1980) and Green et al 1982 respectively.

RESULTS

The H and E stained section of cerebellar cortex form the control rats showed a characteristic appearance of three distinctively arranged layers of cells with a punctate appearance. The outer molecular layer consists of few neuronal cells that appeared prominent. The middle Purkinje cell layer consisting of a monolayer of large spherical-shaped Purkinje cells sandwiched between the outer molecular layer and inner granular layer. The inner granular layer consists of densely packed granular cells. All the three distinct layers and their associated cells appeared distinct and normal in this section (Plate A1).

The H and E stained section of the cerebellar cortex from Group B MSG-treated rats showed cortical distortions of the three cortical layers that are pronounced in the Purkinje cell layer. The purkinje cell layer showed loss of Purkinje cells. Loss of cellular components and degenerative characterized neurons occurred in this section (Plate B1).

The H and E section of the cerebellar cortex from Group C MSG-treated rats revealed increased cortical alterations in form of neuronal loss and degenerative changes in the cortical layers. Degenerative changes and loss of Purkinje cells occurred in this section. Some vacuolations were also observed in this section. The cortical layers appeared to be severely distorted in this treated group (Plate C1).

The H and E stand section from the cerebellar cortex of Group D MSG-treated rat similarly revealed increased loss and degeneration of the cortical layers particularly the Purkinje cell layer. The cortical layers appeared to be distorted and some of the Purkinje cells have been lost in the middle layer. The molecular layer and granular layers showed some distortions and vacuolations of the stroma (Plate D1).

Table 1 and Figure 1 reveal changes in the levels of MDA following MSG expos ure in the neocerebellar cortex of adult Wistar rats. The figure shows a dose-response relationship in the activities of antioxidant enzymes and oxidative parameters.

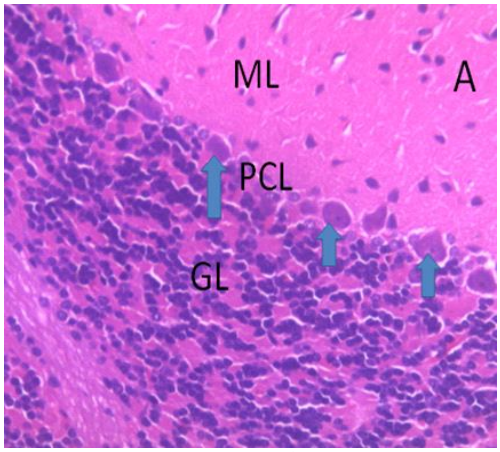
There was a significant ($P < 0.05$) increase in LPO in the group B, C and D compared with group A-control. Lipid peroxidation increased from 25.18 ± 0.70 in group A (Control) to 28.22 ± 0.79 in group B, 30.39 ± 0.43 in group C and 32.40 ± 0.97 in group D MSG-treated rats (Figure 1 and Table 1).

The activity of SOD similarly decreased significantly ($P < 0.05$) in MSG-treated rats compared with the controls (Figure 4.2 and Table 4.3). The activity of SOD decreased from 2.10 ± 0.05 in group A (Control) to 1.60 ± 0.08 in group B, 0.93 ± 0.14 in group C and 0.40 ± 0.04 in group D. The reduction in SOD activity in MSG-treated in cerebellar neocortex of Wistar rats occurred in a dose-dependent manner (Figure 2).

Table 1: Showing the Effects of Oral Administration of MSG on Antioxidant and Parameters in NeoCerebellar Cortical Tissue of Adult Wistar Rats.

Group	Lipid Peroxidation) MDA(nmol/g tissue	Catalase Activity (CAT) (µmol/g tissue)	Superoxide Dismutase (SOD) (µmol/g tissue)	GlutathioneGSH(µn mol)/g tissue)	Nitric oxide (NO) (µmol/g tissue)
A	25.18 ± 0.70	79.57 ± 4.01*	2.10 ± 0.05	43.98 ± 1.85	0.83 ± 0.03
B	28.22 ± 0.79*	65.74 ± 2.15*	1.60 ± 0.08*	31.78 ± 0.41*	1.39 ± 0.12
C	30.39 ± 0.43*	53.85 ± 1.61*	0.93 ± 0.14*	22.38 ± 0.37*	2.46 ± 0.10
D	32.40 ± 0.97*	41.95 ± 2.15*	0.40 ± 0.04*	17.58 ± 0.88*	4.86 ± 0.45

Data are represented as Mean ± SEM *Significant difference when compared with control using t- test at ($P < 0.05$).



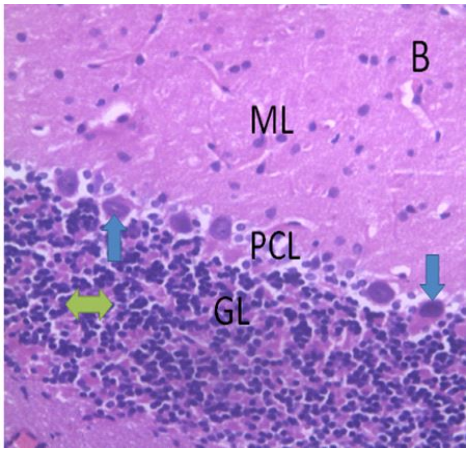
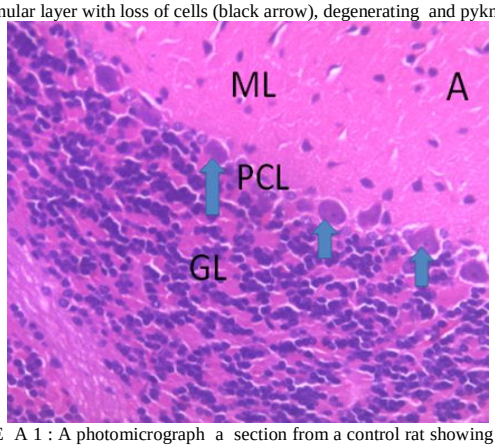


PLATE A 1 : A photomicrograph a section from a control rat showing cerebellar cortex with three cortical layers appearing normal. Note the purkinje cells (green arrow) are arranged in a monolayer (green arrows); purkinje cell layer (PCL) sandwiched between the outer molecular layer (ML) and inner granular layer (GL) . All the three cortical layers appeared intact. H &E X400 Plate B1: A photomicrograph of a section in the cerebellar cortex of MSG-treated rat (2g/kg MSG for 28 days) showing vacuolations and loss of cells in cortical layers particularly the purkinje cells appeared vulnerable. Note the distortion of the granular layer with loss of cells (black arrow), degenerating and pyknotic purkinje cells (green arrows) are surrounded by spaces.



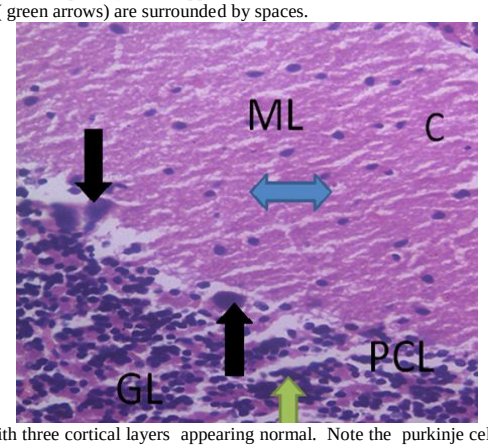
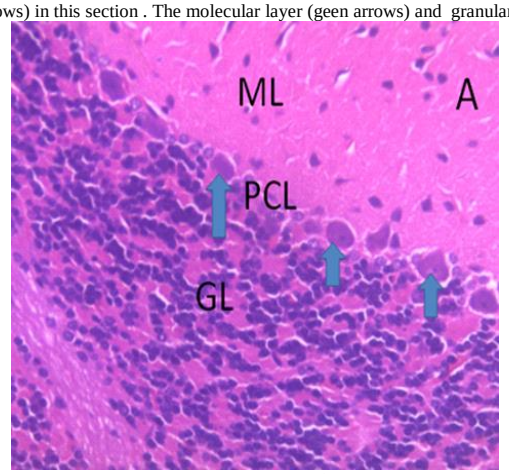


PLATE A 1 : A photomicrograph a section from a control rat showing cerebellar cortex with three cortical layers appearing normal. Note the purkinje cells (green arrow) are arranged in a monolayer (green arrows); purkinje cell layer (PCL) sandwiched between the outer molecular layer (ML) and inner granular layer (GL) Plate C1: A photomicrograph of a section in the cerebellar cortex of MSG-treated rat (4g/kg MSG for 28 days) showing increased vacuolations and loss of cells in cortical layers. Note the enlarged vacuoles in purkinje cell layer ,increasing degeneration, pyknotic and loss of purkinje cells (black arrows) in this section . The molecular layer (geen arrows) and granular layers (green arrow) have irregular outlines H & E X400



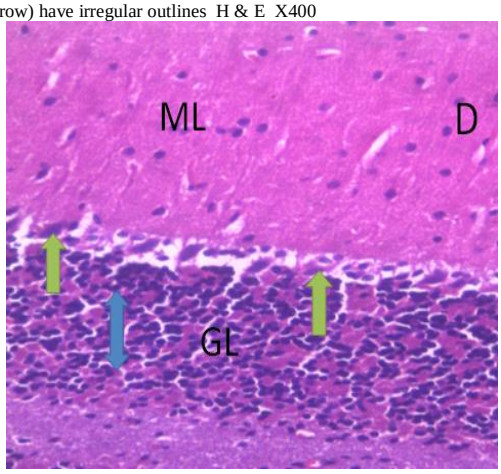


PLATE A 1 : A photomicrograph a section from a control rat showing cerebellar cortex with three cortical layers appearing normal. Note the purkinje cells (green arrow) are arranged in a monolayer (green arrows); purkinje cell layer (PCL) sandwiched between the outer molecular layer (ML) and inner granular layer (GL) Plate D1: A photomicrograph of a section in the cerebellar cortex of MSG-treated rat (6g/kg MSG for 28 days) showing vacuolations, reduced PCL and loss of cells in cortical layers. Note the elongated (shrunken) and degenerating purkinje cells in this section (black arrows). The granular layer is also distorted (green arrow) H & E X 400

The activity of CAT conversely, decreased significantly ($P < 0.05$) in the MSG-treated rats compared with the controls. It decreased from 79.57 ± 4.01 in group A (Control) to 65.74 ± 2.15 in group B, 53.85 ±1.61 in group C and 41.95 ± 2.15 in group D MSG-treated rats (Table 1 and Figure 3).

Table 1 and Figure 4 demonstrate the Mean ± SEM of GSH activity in neocerebellar cortex of Wistar rats following MSG-administration. The GSH activity also decreased in a dose-response relationship in the Wistar rats after MSG treatment (Figure 4).

The GSH activity was 43.95 ± 1.85 in group A (Control) which decreased significantly (P< 0.05) to 31.78 ± 0.41 in group B, 22.38 ± 0.37 in group C and 17.58 ± 0.88 in group D MSG-treated rats. Similarly, the neocerebellar nitric oxide level increased in a dose – dependent manner from 0.83 +-.03 in group A (controls) to 1.390+ 0.12, 2.46 ± 0.10 and 4.86+ 0.45 respectively in MSG – treated group B,C and D Wistar rats.

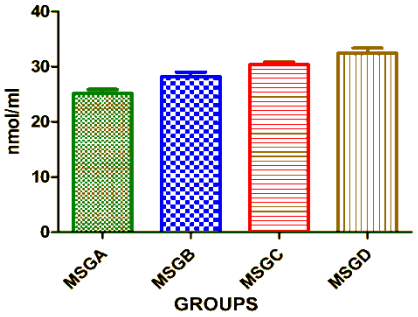


Figure 4.1: Showing the effects of MSG for 28 days on lipid peroxidation in neocerebellar cortex of adult Wistar rats. Each bar represents Mean ± SEM

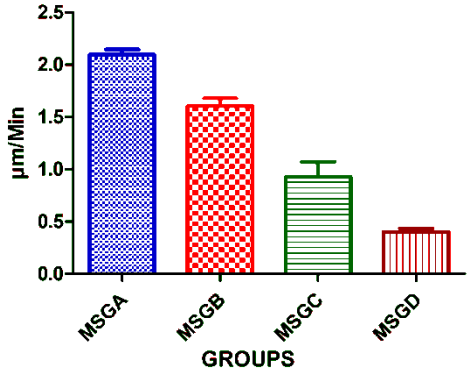


Figure 4.3: Showing the effects of MSG for 28 days on SOD activity in neocerebellar cortex of adult Wistar rats. Each bar represents Mean ± SEM

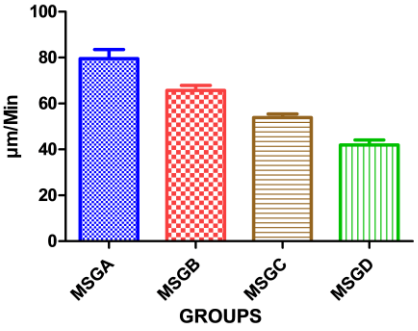


Figure 4.5: Showing the effects of MSG for 28 days on CAT activity in neocerebellar cortex of adult Wistar rats. Each bar represents Mean ± SEM

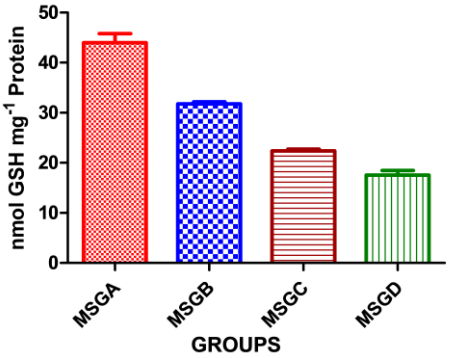


Figure 4.7: Showing the effects of MSG for 28 days on GSH activity in neocerebellar cortex of adult Wistar rats. Each bar represents Mean ± SEM

DISCUSSION

The findings from the present study have shown various histopathological changes in the cortical neurons of cerebellar neocortex in adult Wistar rats following MSG exposures. The histopathological changes in the cortical tissues in MSG-treated rats appeared to be in form of neurodegenerative and atrophic changes in the cortical neurons of the MSG-treated rats and Purkinje and granular cells of the cerebellar cortex appeared pyknotic shrunken, with neuronal loss and vacucuolization. The various histopathological presentations in the MSG-treated sections may be attributed to excitotoxicity induced by MSG in the treated rats.

High doses of glutamate had been implicated in neuroendocrine abnormalities and neuronal degeneration (Moreno et al, 2005) and oxidative damage to different organs (Farombi and Onyema, 2006; Pavlovic et al, 2007). Previous investigation has demonstrated that MSG produces excitotoxicity and induces brain damage (Yu et al, 2006; Zhang et al, 2008,). Additionally, excitotoxicity that is based on the release of excitatory amino acid (EAAs) mainly glutamate is a process by which glutamate or other EAAs induce neuronal cell death in the CNS (Choi, 1990; Choi, 1992), which has been implicated by other investigators in a various acute and chronic degenerative diseases including ischemia, hypoxia, focal and global ischemia traumatic brain injury, Alzheimer's disease, Parkinson's disease, spinocerellar degeneration and amyotrophic lateral sclerosis (Choi, 1988, Whetsell, 1996 and Pelliciari, 1998).

It has been shown that excessive accumulation of glutamate in the synaptic cleft is correlated with excitotoxicity. Excitotoxicity with involves pathological changes in nerve cells lead to neuronal damage and death in response to excessive stimulation by neurotransmitters such as glutamate and similar substances (Abass and El-Haleem, 2011).

Lipid peroxidation (LPO) increased significantly (P < 0.5) in a dose dependent manner in the MSG-

treated rats compared with the control in neocerebellar tissues in this study. The elevation of lipid peroxidation observed in the MSG-treated rats might be due to increase glutamate level which resulted in excitotoxic neuronal cell death through the activation of N-methyl-D aspartate (MDA) and non NMDA glutamatergic receptors in the CNS (Gonzalez-Burgos et al, 2004; Segura-Torres et al, 2006). Additionally, it has been noted that increased lipid peroxidation could also be induced by alteration in redox potential of the concerned cell and thus enhancing lipogenesis (Sushma et al, 2006). The first enzyme involved in the antioxidant defense is SOD. A significant reduction in SOD activity was observed in neocerebellar cortical sections of MSG-treated rats.

The significant decrease in SOD levels in MSG-treated rats may be due to excessive production of ROS (Reactive oxygen species). The excessive release of ROS may attack the thiol group of cysteine residues and PUFAS of biological membranes leading to cell damage (Li *et al*, 2005; Otitoju *et al*, 2008). Previous investigation has shown that reduction in SOD would further increase ROS which ultimately inactivates CAT (Kono and Fridovich, 1982).

This study has noted a significant ($P < 0.5$) decrease in the catalase (CAT) activity in the cerebral motor cortex of MSG-treated rats compared with controls. Previous investigation on the CAT activity on the cerebrum of the mice has similarly noted a similar decrease in CAT activity after MSG-administration (Adebayo et al, 2011). The significant reduction in the CAT activity has been attributed to reduced availability of NADPH, as availability of MSG favours lipogenesis by increasing the level of glutamine (Chondhary et al, 1996; Abdel Baky et al, 2009).

The significant decrease in in neocerebellar and neocerebral motor cortical CATs in a dose-dependent manner in the MSG-treated rats in this study is in accordance with the report of Singh et al (2003) who investigated the effect of I.P MSG administration for 6 consecutive days on mitochondrial lipid peroxidation and antioxidant status in adult rat cerebral hemisphere after 30 and 45 days. The reports of Farombi and Onyema (2006) and Noor and Mourad (2010) on CAT who administered MSG through I.P. injection to adult rats consecutively for 10 and 6 respectively are also in agreement with the present report. Increased production of free radicals has been implicated in depletion or inactivation of CAT activity Kono and Fridorich (1982). The significant decrease in the level of CAT in layer V and cerebellar cortical layers in MSG-exposure rats may partly be due to excessive production of superoxides anions after MSG exposure. The report of this study has indicated a significant decrease in MSG-treated groups compared with the control group. The decrease in CAT level may be due to excessive production of superoxides anions following MSG-exposure

Glutathione (GSH) is a tripeptide composed of glutamate, cysteine and glycine which plays a critical role in protecting cells from xenobiotics and oxidative damage (Noor and Mourad, 2010). GSH has the potentials to act as an antioxidant in many ways; it can react non-enzymatically with superoxide (Winterbourn and Metodiewa; 1994), nitric oxide (Claney et al, 1994), hydroxyl radical (Bains and Shaw, 1997), and peroxynitrite (Koppal et al, 1999). GSH therefore, functions directly as a free radical scavenger (Noor and Mourad, 2010). Report from previous investigators has shown that glutamate toxicity involves an imbalance in the homeostasis of cysteine, the precursor of GSH, leading invariably to depletion of intracellular GSH levels coupled with reduced ability to protect cells against oxidative reactions and injury in the cell and ultimately cell damage (Yaqub et al, 2008) and cell death, (Maher and Davis 1996). Furthermore, it has been reported that lipid peroxidation may eliminate the active sulfhydryl group of GSH and other enzymes (Yaqub et al, 2008). A significant increase ($P < 0.05$) in lipid peroxidation was observed in the neocortical tissues of MSG-treated rats. It has been noted that increased ROS could lead to depletion of GSH pool and the decrease in cellular GSH level pool further enhances oxidative stress (Sharma et al, 2014). Report has shown that NO has a double edged knife in relation to pathophysiology in that both the paucity and abundance of NO induces various diseases (Kim et al, 2002). Furthermore, previous studies have indicated that direct toxicity of NO is enhanced by reacting with superoxide radical such as peroxynitrite which is capable of oxidizing cellular structure which consequently results in lipid peroxidation, a process leading ultimately to membrane damage (Weinsteineal, 2000). The dose – dependent increase in NO level in MSG – treated rats occurred concomitantly with dose dependent increase in lipid peroxidation (LPO) in MSG – treated rats. In other words, the dose – response relationship in association with elevation of NO and lipid peroxidation level in MSG – treated rat in this study may be another explanation induced by MSG in this study.

Again, it has been reported also that several mediators of systemic vasodilatation such as NO is associated with some particular diseases (Nasser et al, 2003).

Additionally, the activity of NO in the brain has been implicated in the pathological conditions such as epilepsy, stress, diseases and side effects of some therapeutic agents (Vanaga and Perumal, 2011).previous investigation has shown that elevated glutamate concentrations might be a

consequence of a NO – mediated mechanism as NO has been shown to increase the release of glutamate from glia and neuron leading to excitotoxicity (Brown et al., 2003).

Conclusion, this study concluded that prolonged exposure to MSG may lead to neocerebellar cortical damage which might be due to oxidative stress induced by excitotoxicity of MSG and consequently , the cerebellar functions might be compromised. We recommend further studies in this regard to corroborate this report.

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