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Research Article

Biochemical Changes In The Brain Of Malnourished Rats Fed Low Dose Monosodium Glutamate.

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Abstract

Monosodium glutamate (MSG) is a non-regulated flavour enhancer with a controversial safety record following lack of intensive and realistic toxicity studies especially under well-defined physiological conditions. Well-fed or malnourished rats (females and males in equal number) were fed low dose MSG (1.6 mg/kg) in aqueous medium by gavage for 35 days. Biochemical indicators of oxidative stress were measured in the rat whole brain homogenates. Statistical analysis was carried out using ANOVA. $P < 0.05$ was taken as statistical significance. The results of the experiments showed that MSG did not produce as much oxidative stress as malnutrition; MSG merely potentiated the oxidative effect of malnutrition in the rat brain. Gender did not produce a profound oxidative effect. Oxidative stress underlies many of the non-communicable diseases such as diabetes, cancers and neurodegeneration. It is concluded that MSG when consumed at as low as the studied dose is unlikely to cause neuronal oxidative damage in the rats.

INTRODUCTION

Monosodium glutamate (MSG) is a well-known flavor enhancer which produces the fifth basic taste called "umami" after bitterness, saltiness, sourness and sweetness (1). The consumption of MSG continues to increase globally (2). However, the safety record of this additive appears contentious (3; 4; 5; 6; 7). Some preclinical and clinical studies have challenged the safety consideration since MSG has been implicated in certain metabolic disorders (7). Prolonged parenteral administration of MSG in rodents was reported to alter glucose metabolism through loss of pancreatic β-cells (9). Similarly, MSG has been implicated in the generation of obesity in experimental animals (10). Literature search shows that the reported toxicities linked with MSG consumption occurred at very high doses (11; 12; 13). These doses are nutritionally irrelevant and are thought of capable of overwhelming normal hepatic metabolism which will ultimately lead to the toxicities. The idea of specifying condition at which MSG is exposed to the subjects which is at variance with the suggestion of (14) would assist in the correct risk assessment of this flavor enhancer (15; 16). Recently (17) reported brain damage in rats exposed orally to the dose of 40 mg MSG/kg for 28 days. This dose can be regarded as toxic (14; 18). Following the controversies surrounding the toxicity of MSG, the present study decided to investigate the oxidative effect of ingesting chronic dose of MSG in aqueous medium in the brain of malnourished rats (17). Malnutrition in the rats has been induced through dietary manipulations primarily by altering protein intake (19). Under malnutrition, growth and body functions are compromised (20) which could affect MSG metabolism.

MATERIALS AND METHODS

Experimental animals

Twenty apparently healthy albino rats average weights 160 ± 2.4 g and 155 ± 1.7 g female and male respectively, were separately housed in standard plastic animal cages. They were exposed to 12 hours light and 12 hours darkness on standard animal feed pellets and potable water. All the rats were subjected to 2 weeks acclimatization period prior

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to the experiments. The animals' body weights and other behavioural activities of the rats were monitored during this period. Commercial MSG was procured from the city grocery supermarket. It was dissolved in distilled water for oral administration to the rats according to the schedule below. All chemicals/reagents used for the experiments were of analytical grade.

Experimental Rat Groups

A total number of forty apparently healthy albino rats, males and females in equal number were randomized into four main groups, each group contained five rats. The groups consisted of malnourished rats only (MN), malnourished rats dosed with MSG (MM), well-fed rats dosed with (WM) or without (WF) MSG. The four groups were replicated for each gender. The well-fed rats were placed on regular rat chow and potable water *ad libitum*. The malnourished rats were placed on a formulated diet and potable water *ad libitum*. The MM and WM rat groups were orally administered 1 ml. aqueous solution of MSG at 1.6 mg/kg body weight daily for 35 days. Protein energy malnutrition was induced in the MN and MM rats by feeding them with low protein isocaloric diet (21) *ad libitum* and potable water throughout the duration of the experiments.

Animal Sacrifice and Collection of Brain Samples

On the 36th day post- treatment, the rats were weighed, sacrificed and the whole brain harvested. The brain was weighed and immediately homogenized in 0.25 M Tris.HCl - sucrose buffer solution pH 7.4 using teflon-lined homogenizer in an ice bath.

Biochemical analyses

Superoxide dismutase (SOD) activity was determined according to the colorimetric method of Misra and Fridovich (22) based on the half inhibition by SOD of epinephrine autoxidation to adrenochrome which absorbs at 480 nm at basic pH 10.2. The decrease in absorbance was monitored for 5 minutes at 30 seconds intervals on the spectrophotometer. MDA, the product of lipid peroxidation was estimated by the colorimetric technique reported by Kumar *et al.,* (23). The absorbance of the pink coloured TBA-MDA complex was read at 535nm. Protein concentration in the samples was estimated using the Folin-Phenol reagent method of Lowry *et al.,* (24), bovine serum albumin was used as the standard protein. Succinate dehydrogenase (SDH) activity was determined using the spectrophotometric method of Munujos *et al.,* (25). The method is based on the reduction of iodonitrotetrazolium chloride (INT) to formazan which absorbs maximally at 500 nm. Colour was developed at 30 oC recorded for 6 min at one minute interval. The absorbance of the reddish coloured formazan was read against blank which contained all the reactants except succinate. The extinction coefficient (ε) is 19,300 M^{-1} cm^{-1} '

Statistical Analysis

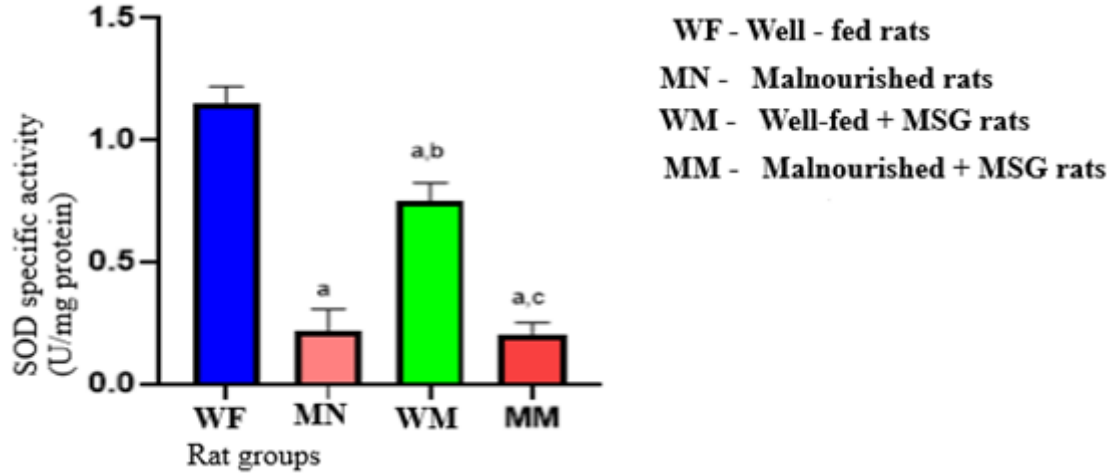
Data were analyzed using one way analysis of variance on GraphPad prism software. Statistical significance was taken at $p < 0.05$. Values are expressed as Mean ± SEM.

RESULTS

All the test rats namely, MN, WM and MM in both males (**Fig. 1a**) and females (**Fig. 1b**) showed reduction in the SOD specific activities in their brains when compared with the respective well-fed rats. Among the well-fed male rats (WF and WM) (**Fig. 1a**), significantly large difference in the specific activity of the enzyme was recorded unlike between the malnourished rats (MN and MM) which the difference though significant but not large. There was a clear departure from this trend among the female counterparts (**Fig. 1b**). The female rats exposed to MSG (WM and MM) showed significantly large difference when compared with their non-exposed counterparts (WF and MN respectively). As with SOD specific activity, the concentration of reduced glutathione (GSH) among the male and female test rats namely, WM, MN and MM was lower than the well-fed rats (WF) (**Fig. 2a,b**). Malnutrition and MSG in concert produced the observed increase in malondialdehyde (MDA) concentration in both genders, but the MSG effect was more pronounced in the males (**Fig. 3a**) than in the females (**Fig. 3b**).

Figure 1. Superoxide dismutase specific activity in the brain homogenates of male (Figure 1a) and female (Figure 1b) rats orally exposed to MSG. a, b, c showing statistical significance when compared with WF, MN and WM respectively.

(a)



(b)

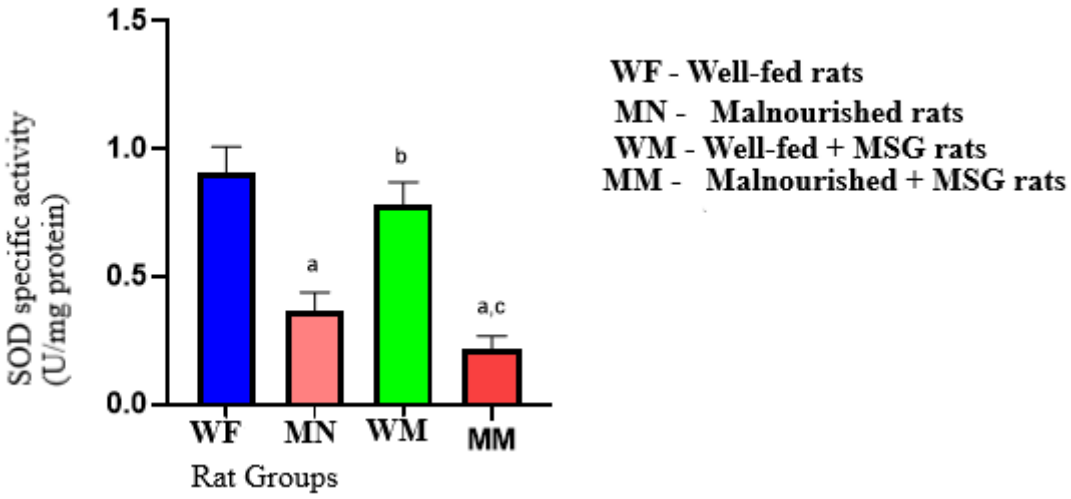
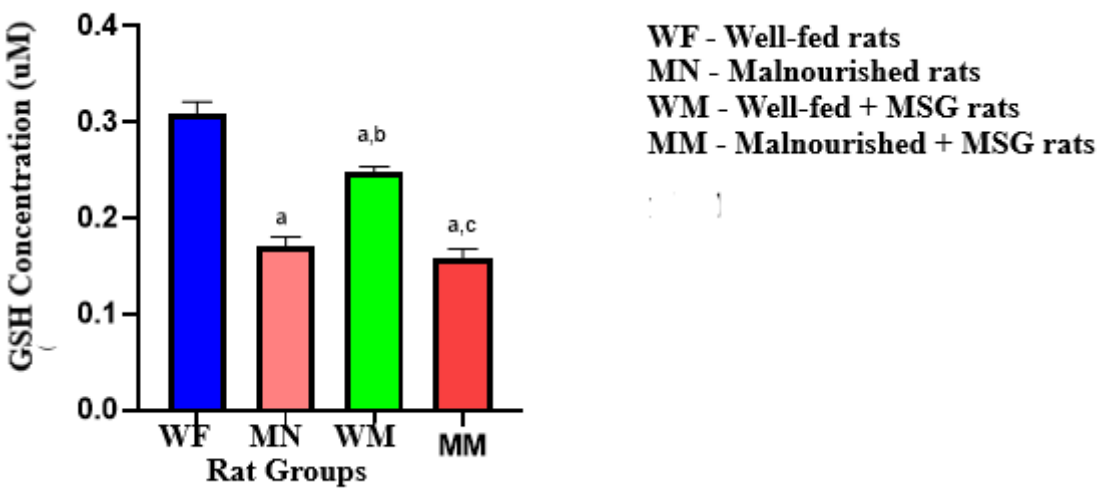


Figure 2. Rat brain reduced glutathione (GSH) concentration in males (a) and females (b) exposed orally to monosodium glutamate. a, b, c, showing statistical significance when compared with WF, MN and WM respectively.

(a)



(b)

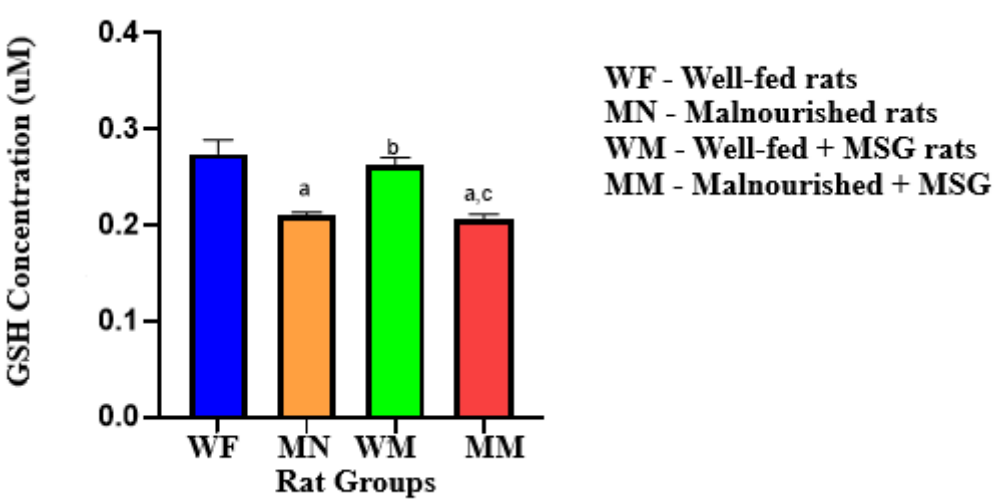
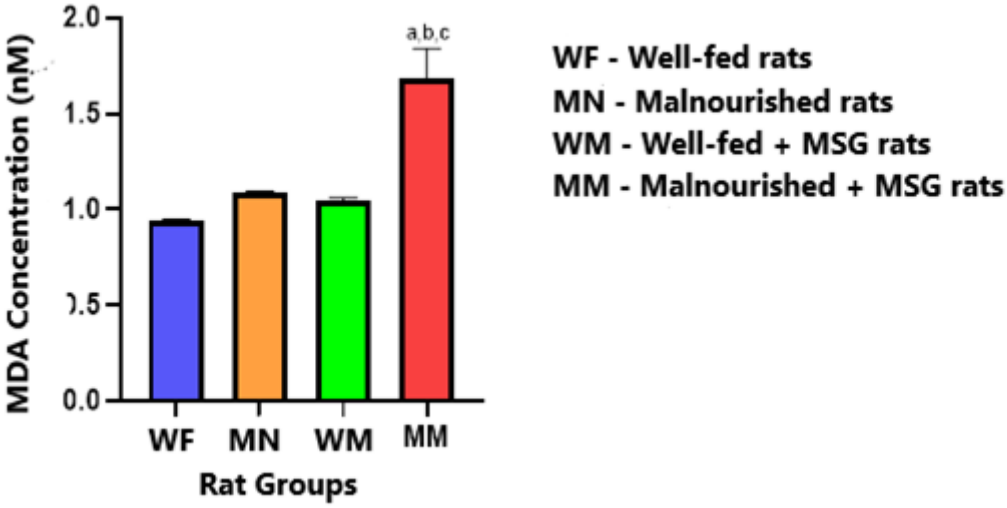
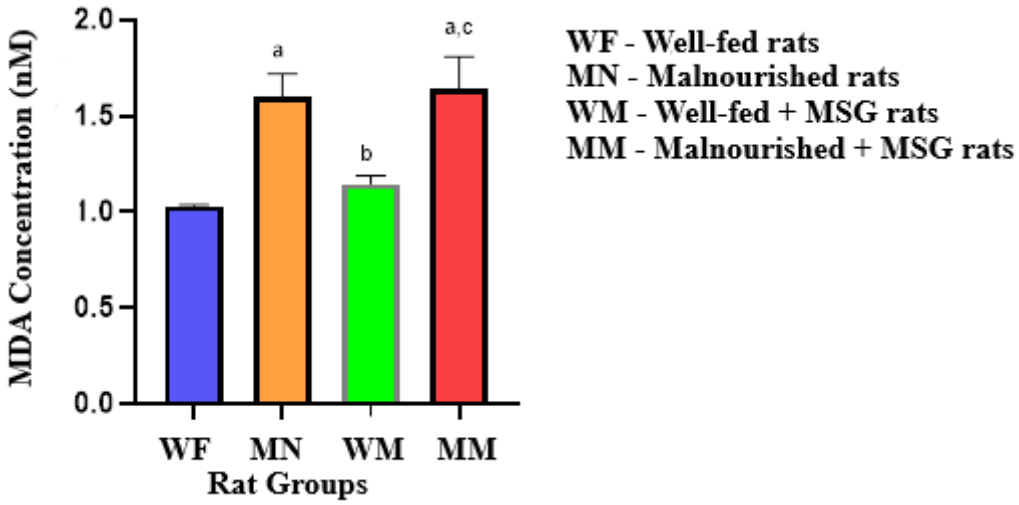


Figure 3. Rat brain malondialdehyde (MDA) concentration in (a) males and (b) females orally exposed to monosodium glutamate. a, b, c, showing statistical significance when compared with WF, MN and WM respectively.

(a)

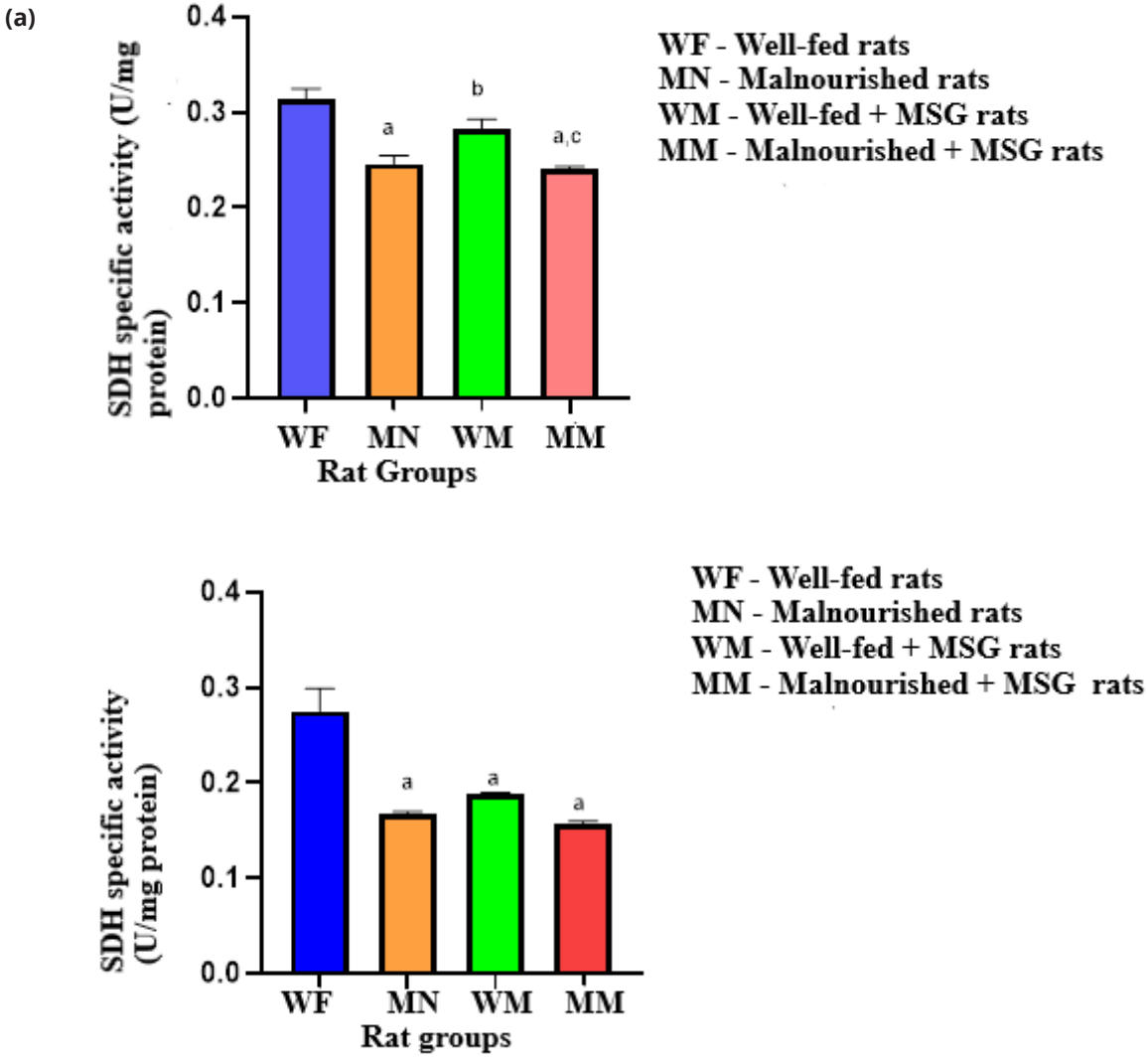


(b)



Generally, the results as they appear in **Figs. 4a** and **4b** showed that the specific activity of succinate dehydrogenase in the rats whole brain homogenates was higher in male rats than in female rats. In the male rats, the observed reduction in the specific activity of SDH among the WM was not statistically significant when compared with the unexposed counterparts (WF) whereas the reductions observed among MN and MM groups were significant compared with the WF (**Fig. 4a**). The specific activity of SDH in WM was significantly higher than in MM. In the female rats (**Fig. 4b**), the changes (reduced specific activity of SDH) observed among the test rats namely, MN, WM and MM were only significant when compared with the well-fed none exposed rats (WF). This is a significant departure from the male counterparts.

Figure 4. Brain Succinate dehydrogenase (SDH) specific activity in (a) male and (b) female rats orally dosed monosodium glutamate (MSG). a, b, c represent statistical significance when compared with WF, MN and WM respectively.



DISCUSSION

Monosodium glutamate is the sodium salt of nutritionally non-essential amino-acid. It is naturally present in certain foods of animal and plant origins (26) as well as an additive in foods (27). MSG is not regulated in most countries leading to abuse which could be responsible for the reported toxicities in human (28; 29; 30). Glutamate is the main excitatory neurotransmitter in the body. Multiple glutamate transporters and receptors are present in the nervous system (31) and possibly accumulate in the brain. Previous studies on the adverse effects of MSG in experimental animals were based on large doses lacking in practicability under normal exposure. The dose applied in this experiment, approximately a tenth of Chinese daily consumption (32), can be generally regarded as safe (18; 33) as it is not deemed to overwhelm normal hepatic metabolism (27). However, increased blood level of MSG and thus adverse effects has been reported when consumed at high dose solely in aqueous medium (14; 34). The

loss of activity of SOD in the test (MSG and malnourished) rats showed that both the MSG consumption and malnutrition were responsible. SOD is an antioxidant enzyme which catalyzes the dismutation of superoxide anions believed to peroxidize membrane lipids (35; 36) thereby protecting against tissue oxidative damage. The peroxidation of membrane lipids compromises its permeability characteristics. The loss of the enzyme activity in both male and female rats probably indicated onset of oxidative stress occasioned more by malnutrition than by MSG consumption. Earlier work (37) on MSG neurotoxicity supported the reduced SOD activity in the rat brain accompanied by loss of nervous co-ordination at a dose five times higher than the present dose. Gender may have played a role in the differential reduction of SOD activity in the rat brain. GSH is a non-enzymic antioxidant molecule. Similarly, the recorded GSH reduction in all MSG-exposed as well as malnourished rats probably meant onset of oxidative stress mediated by GSH depletion (38; 39). Lipid peroxidation, a fingerprint of oxidative stress is an enzyme catalyzed reaction involving free radicals in biological systems. MDA (1,3-propanedial) is the product of peroxidation in the cells and the increased level suggested oxidative stress in the brain (40). It is possible that both MSG and malnutrition individually or in concert induced neuronal cyclooxygenase-2 (41) leading to the generation of superoxide free radicals and ultimately oxidative stress (42). Reactive chemical species production in the absence or shortage of endogenous antioxidants, results in oxidative stress usually stimulating various cell signaling pathways and inflammatory cytokines involved in cell damage. Oxidative stress is thought to underlie the pathogenesis of certain non-communicable diseases including diabetes, cancers and neurogenerational diseases (43) occasioned by modification of the biomolecules by way of glycoxidation, DNA oxidation, protein and or side chain oxidation as well as lipoxidation (44; 45). SDH is a flavoprotein intermediate in the citric acid cycle located in the inner leaflet of the mitochondria. It is a key enzyme in energy transduction. Change in the activity of the enzyme has been related with certain diseases such as hypertension, cancers, neuromuscular diseases and mitochondrial dysfunction (46; 47).

CONCLUSION

The chronic oral administration of MSG in aqueous solution to rats did not induce oxidative stress in the whole brain homogenates as much as malnutrition did. MSG potentiates oxidative effects in malnourished female and male rats but gender did not produce profound oxidative effects in the rats' brain.

Ethical approval

All animals used were approved by Ladoke Akintola University of Technology Animal Care and Research Ethics Committee.

Competing interests

We declare no competing interest in this present study.

Authors' contributions

The Authors contributed equally in this present study in the conception, design, execution, interpretation of research findings and article writing.

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