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Full Length Research Paper

Influence of sub-chronic oral exposure to high monosodium glutamate on some serum markers of the renal functions in male Wistar rats

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Monosodium glutamate (MSG) is a flavor enhancing food additive that may be present in packaged food without appearing on the label. This could increase the possibility of its inadvertent consumption in high concentration. The study investigated the effects of MSG on some serum markers of renal functions in adult male Wistar rats by daily oral exposure to 3 ml kg^{-1} dose distilled water (DW) and 15 mg kg^{-1} MSG for 4 weeks. In the serum, MSG treatment significantly ($p < 0.05$) decreased urea and creatinine concentrations, whereas it markedly increased the computed urea to creatinine (Urea: Creatinine) ratio. The results appear to suggest that exposure to MSG (15 mg kg^{-1}) significantly altered the renal functions in rats by way of compromised urea and creatinine metabolism. The nutritional and health implications of the results may be significant in animals and therefore warrant further and better controlled investigation in humans.

Key words: Monosodium glutamate, Wistar rats, renal functions, urea, creatinine.

INTRODUCTION

Monosodium glutamate (MSG), the sodium salt of glutamate, is a flavor enhancing food additive that may be present in packaged food without appearing on the label. In Nigeria, MSG is sold in most foodstuff markets and stores.

According to WHO report, the average daily intake of MSG in enlightened society is about 1.0 g (Marshal, 1994) but with the increasing consumption of MSG in Nigeria, either in packaged foods or in dishes, the daily intake in Nigeria may be exceeding 1.0 g. This is particularly disturbing in the light of reports of MSG-induced adverse effects in animals, including seizure (Gonzalez-Burgos et al., 2004); possible liver damage (Egbuonu et al., 2009a, 2010a) and enhanced appetite and food intake that could lead to obesity (Rogers and Blundell, 1990; Mozes et al., 2004; Egbuonu et al., 2010b). Other reported adverse influence of MSG in animals include impaired cholesterol metabolism (Egbuonu et al., 2010b); damage to the arcuate nucleus of the brain (Belluardo et al., 1990); oligospermia and possible male infertility (Onakewhor et al., 1998) and reduction in the locomotor activites (Eweka and Om'Iniabohs, 2008). In addition, the possible induction of prostate pathologies by varying concentrations of MSG in rats was recently reported (Egbuonu et al., 2010c), suggesting possible dose dependent influence of MSG on prostate patho-logies of animals.

Indeed, the alternative use of MSG as laundry bleach could be a pointer that its possible bleaching properties may elicit adverse response in animals especially when taken in high concentration. The kidney is among the major organs of the body and, the consumption of MSG in high concentration may affect its vital function of glomerular filtration, resulting in severe pathologies. The effect on the renal function of animals following ingestion of high concentration of MSG in animals, to the knowledge

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Abbreviations: WHO, World Health Organization; **MSG,** monosodium glutamate; **DW,** distilled water; **ANOVA,** analysis of variance; **SPSS,** Statistical Package for the Social Sciences.

of the authors, is lacking. Thus, the present study aimed at examining the possible effects of ingesting high concentration of MSG on some serum markers of the renal functions in rats. To achieve the stated aim, serum urea and creatinine concentrations were determined by standard methods and the serum urea to creatinine (urea: creatinine) ratio calculated from the corresponding results obtained in the present study.

MATERIALS AND METHODS

Ajinomoto, a brand of monosodium glutamate marketed by West African Seasoning Company Limited, was bought from a daily market at Nsukka, Nigeria. Other chemicals were of certified analytical grade and were used without further purification.

The animal study was conducted in accordance with the protocols approved by the local experimental animal ethics committee. Eight adult male Wistar rats with mean body weight of 68.30±0.5 g bred at the animal house of the Faculty of Biological Sciences, University of Nigeria, Nsukka, were kept in clean stainless steel cages and in a well-ventilated house with free access to standard feed and drinking tap water. The animals were kept at room temperature (28±2°C) with a 12 h daylight/dark cycle under humid tropical conditions. After the adaptation period of a week, the rats were randomized into two groups (n = 4). The control group (Group I) received distilled water (3 ml kg^{-1} dose) whereas Group II received monosodium glutamate (15 mg kg^{-1} dose). The treatment was per oral and daily for 4 weeks.

After 4 weeks, the blood sample of the rats was collected individually by methods described previously (Egbuonu et al., 2009a, b). In summary, all the rats were sacrificed the next day, following an overnight fast. Blood sample of each rat was collected by puncturing the ophthalmic venous plexus with sterile capillary tubes directed into labeled centrifuge tubes. The blood thus collected was allowed to clot after standing for 10 min at ambient temperature. Thereafter, the serum was separated by centrifugation at 3000 *xg* for 10 min.

Determination of serum urea concentration

The serum urea concentration was determined by the method of Alexander and Griffith (1992) based on the principle that ammonia (from the urease catalyzed hydrolysis of urea to ammonia and carbon dioxide) is converted to indophenols blue in the presence of sodium nitroferricyanide-phenol and hypochlorite reagents. The absorbance was read with a spectrophotometer set at 625 nm.

Determination of serum creatinine concentration

On the other hand, the serum creatinine concentration was determined by the method of Wilding and Kennedy (1977). To 0.1 ml of serum sample in a test tube, 0.8 mL of acid tungstate was added. The content was shaken and centrifuged. The resultant supernatant was aspirated into another test tube. Then, 0.2 ml of picric acid and 0.1 ml of sodium hydroxide (NaOH) (1.4 mol L^{-1}) were added into the tube and the absorbance read at 500 nm.

Statistical analysis

All data collected were analyzed by one-way analysis of variance (ANOVA) as described (Egbuonu et al., 2009b) using the Statistical Package for the Social Sciences (SPSS version 11; SPSS Inc., Chicago, IL., USA). Data in the text and tables are presented as means and standard errors of the mean. Significance was accepted at $p < 0.05$.

RESULTS AND DISCUSSION

Urea and creatinine are bio-indicators of the renal function (Kaplan et al., 1988) and the underlying presence of component(s) of the metabolic syndrome (McDonald et al., 2003) currently noted to predispose animals to high risks of colorectal cancer (Siddiqui, 2010; Pelucchi et al., 2010). Hence, imbalance in their physiological homeostasis could evoke pathological conditions. In comparison with the control, MSG treatment significantly decreased the serum urea concentration (5.09 ± 0.09 mg 100^{-1} ml, representing a reduction of 96.58%) (Table 1), and the serum creatinine concentration (7.545 ± 0.15 mg 100^{-1} ml, representing a reduction of 22.76%) (Table 2). The results could be suggestive of either down-regulation in the synthesis of urea and creatinine or their enhanced excretion through urine, perhaps in response to possible MSG-induced toxic assault on the kidney and consequent impairment of its functional capacity. This appears to support the report of possible adverse response on the liver and other major organs (including the kidney) following high ingestion of MSG in rats (Egbuonu et al., 2010a).

In particular, decreased serum creatinine concentration as observed in the present study may be predictive of glomerular hyperfiltration associated with increased metabolic risk (Tomaszewski et al., 2007), including diabetes (Wilson et al., 2005; Lorenzo et al., 2009; Harit et al., 2009; Hjelmesæth et al., 2010). Serum creatinine is a surrogate marker of muscle mass that is associated with insulin resistance and metabolic syndrome (Yonemura et al., 2004). And recently, a relationship between low serum creatinine and type 2 diabetes mellitus was demonstrated in non-obese middle-aged Japanese men (Harita et al., 2009) and a population of Caucasian subjects (Hjelmesæth et al., 2010), seemingly suggesting possible induction of type 2 diabetes mellitus in animals following daily ingestion of MSG in high concentration.

Furthermore, the nonphysiologic urea concentrations were associated with increased levels of reactive oxygen species and the oxidative stress marker 8-oxoguanine in cultured cells, probably due to urea potential to increase carbamylation as well as carbonylation (Zhang et al., 2004). Therefore, it seems likely that the significant decrease in urea observed in this study might have altered the function of cytosolic, nuclear, and mitochondrial proteins involved in the regulation of mitochondrial reactive oxygen species production. The possibly enhanced production of the reactive oxygen species could be renotoxic consequently impairing the functional capacity of the kidney.

The kidney is among the major and important organs of animals and its compromised functional capacity might present with severe pathologies thus, warranting caution in daily high intake of MSG in animals. The present results

Table 1. Effect of DW and MSG on the serum urea concentration.

Measurement	Urea (mg 100^{-1}ml)	
	DW (I)	MSG (II)
Mean	5.27	5.09*
SEM	0.06	0.09
Relative mean (%)	100	96.58
Difference in mean relative to control (%)		−3.42

Results are mean ± SEM (n = 4); *Significantly different from control ($p < 0.05$).

Table 2. Effect of DW and 7MSG on the serum creatinine concentration.

Measurement	Creatinine (mg 100^{-1}ml)	
	DW (I)	MSG (II)
Mean	33.13	7.545*
SEM	0.13	0.15
Relative mean (%)	100	22.76
Difference in mean relative to control (%)		−77.24

Results are mean ± SEM (n = 4); *Significantly different from control ($p < 0.05$).

Table 3. Influence of DW and MSG on the serum urea: creatinine ratio.

Measurement	Urea: Creatinine ratio	
	DW (I)	MSG (II)
Mean	0.16	0.68*
SEM	0.03	0.25
Relative mean (%)	100	425
Difference in mean relative to control (%)		+325

Results are mean±SEM (n = 4); *Significantly different from control ($p < 0.05$).

however seem at variance with the reported possible nephroprotective potential of MSG (Egbuonu et al., 2009a) where, but a relatively lower concentration of MSG (5 $mgkg^{-1}$ BW) was used. This may suggest that, in contrast to low concentration, MSG at high concentration could be renotoxic. In apparent support of the present study, Vinodini et al. (2010) reported that MSG exposure to rats probably exerted adverse effect on the renal function following, perhaps, MSG-induced oxidative stress on the renal tissue.

To obtain further diagnostic information as suggested by Egbuonu et al. (2010d), we computed the serum urea: creatinine ratio. Data showed that MSG treatment significantly increased the computed serum urea: creatinine ratio by 0.68 representing over three-fold increase (325%) when compared with the control rats (Table 3). This appears to indicate excessive protein turnover due to hemorrhage (Raphael, 1983) perhaps from the gastrointestinal tract (Witting et al., 2006). In addition, the observed increase in serum urea: creatinine ratio could be reflective of decreased muscle mass (Feinfeld et al., 2002), probably due to the abnormal protein catabolism and the induction of diabetes suggested in the present study. In abnormal protein catabolism associated with non insulin dependent diabetes mellitus (type 2 diabetes mellitus), protein in the form of hemoglobin could be broken down (by digestive enzymes of the upper gastrointestinal tract) into amino acids which are then reabsorbed in the gastrointestinal tract and broken down into urea (Charlton and Nair, 1998) and creatinine for onward excretion via urine. This may have resulted in the depletion of serum urea and creatinine concentrations as observed in the present study.

Taken together, the results appear to suggest that exposure to MSG (15 mg kg^{-1}) significantly altered the renal functions in rats by way of compromised urea and creatinine metabolism. The renal function of glomerular filtration is critical to animal health. Thus, the results of this study may be significant to animal health hence warrant further and better controlled investigation in humans.

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