THE EFECT OF CONSUMPTION OF MONOSODIUM GLUTAMATE ON GROWTH HORMONES AND RENAL FUNCTIONS IN ADULT WISTAR RATS.

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Abstract: Monosodium Glutamate (MSG) is utilized as a food additive to improve food's characteristics. Wistar rats were acclimated for two weeks and then divided into four groups. Group A was the control and received only rat chow and water. Groups B, C, and D were given low, moderate, and high doses of MSG, respectively, for 60 days. There was decline of growth hormones level of B, C, and D when compared with group A. For the antioxidant enzymes of group B, C, D compared with Control group A, there was increase in CAT and MDA but decrease in SOD, GSH. For the histological features of group B, C, D there PCT, DCT, CS and epithelial cells are degenerated and constricted compared with control group A that are properly differentiated and organized. Data obtained from this result suggested that intake of high concentration of MSG can impair renal functions and cause histological damage to the kidney morphology. It can cause decline in growth rate. MSG can heighten stress response and induce Oxidative stress.

Keywords: Monosodium Glutamate (MSG), Kidney Failure, Oxidative stress, Growth Retardation.

Introduction

Compounds added to food products with the intention of preserving flavor, enhancing taste, or improving appearance are known as food additives. Monosodium glutamate (MSG), is a food addictive and sodium salt of naturally occurring non-essential amino acid (Tawfik and Al-Badr, 2012). MSG contains 78% glutamic acid, 22% sodium and water (A. Samuels, 1999.). Glutamate is one of the most common amino acids found in nature and is the main component of many proteins and peptides of most tissues. Glutamate is also produced in the body and plays an essential role in human metabolism. It is a major component of many protein - rich food products either in free or bound state of animal such as meat, fish, milk and cheese or vegetable origins such as mushroom and tomato (IFIC, 1994.). In general, the natural glutamic acid found in food does not cause problems, but the synthetic free glutamic acid formed during industrial processing is a toxin. Some of the common well know synthetic brand product are; AJINOMOTO, VETSIN, ACCENT etc.

MSG is commonly used as a flavor enhancer especially in Chinese, Thainese and Japanese foods (K. Ikeda 1917; FDA, 1995.). When MSG is added to food, it provides a flavoring function similar to the naturally occurring free glutamate which differ from the four classic tastes of sweet, sour, salty and bitter (A. Leung and S. Foster, 1996.). As food additive, MSG is described and listed on food labels as a " Flavoring " or " hydrolyzed vegetable protein ". Through its stimulation of the orosensory receptors and by improving the palatability of meals, MSG influences the appetite positively, and induces weight gain. Despite its taste stimulation and improved appetite enhancement, reports indicate that MSG is toxic to human and experimental animals (D. Biodun and A. Biodun, 1993.). MSG could produce symptoms such as numbness, weakness, flushing, sweating, dizziness and headaches. In addition to these MSG symptom complex, ingestion of MSG has been alleged to cause or exacerbate numerous conditions, including asthma, urticaria, atopic dermatitis, ventricular arrhythmia, neuropathy and abdominal discomfort (R. S. Geha et Al., 2001). MSG has a toxic effect on the testis by causing a significant oligozoospermia and increase abnormal sperm morphology in a dose - dependent fashion in male Wistar rats (J. U. E. Onakewhor et al., 1998.). It has been implicated in male infertility by causing testicular hemorrhage, degeneration and alteration of sperm cell population and morphology (I. A. O. Oforofuo et al., 1997.). It has been reported that MSG has neurotoxic effects resulting in brain cell damage, retinal degeneration, endocrine dis order and some pathological conditions such as addiction, stroke, epilepsy, brain trauma, neuropathic pain, schizophrenia, anxiety, depression, Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis (A. Samuels, 1999.). It cannot be stated that MSG is the cause of such varied conditions as epilepsy and Alzheimer's disease, although there may be concerns of its involvement in its etiology (A. Samuels, 1999). The Food and Drug Administration (FDA) of the United States reports that MSG is safe and that it should be maintained on the " Generally Recognized as Safe " (GRAS) -list of foods. MSG is thus reportedly permitted as a safe food additive that needs no specified average, daily intake or an upper limit intake requirement (P. P. Rogers and J. E. Blundell, 1990.).

The Kidney is a paired organ located in the posterior abdominal wall, whose major functions include the removal of toxic metabolites and waste products from the blood and regulation of the amount of fluid and electrolytes balance in the body. To test functions of the kidneys routine urinalysis is used to measure serum urea, creatinine, sodium and potassium and serum bicarbonate (L. Stryer ,1996; R. Montgometry et al 1990; C. Burtis and E. Ashwood 1999, Merck and Co., 2004.).

Material and methods: Ethical Concerns in Animal Study: All the animal experiments and protocol were maintained according to the rules and regulations of National Institute of Health (NIH, (2011) for laboratory animal care and use. Ethical clearance was obtained from the Olabisi Onabanjo

University Teaching Hospitals Health Research Ethics Committee (OOUTH- HREC) with approval number OOUTH/HREC/652/2023AP. All the animal carcasses were buried deep in the ground covered with lime and disinfectant at least two feet beneath the natural surface and covered with soil.

Experimental Design and Treatment: Forty healthy adult male Sprague- Dawley rats weighing about 70 and 100 g were used for this experiment. The rats were allowed to acclimatize for a period of two weeks; the animals were housed at normal environmental condition at the animal house, Obafemi Awolowo College of Health Sciences, Sagamu, Ogun State, Nigeria. The rats were placed on pelleted diet and water ad libitum during the period of acclimatization and throughout the period of the experiment. The animals were weighed and randomly assigned to groups as shown in the 1 table below, Administration of MSG was done daily for 60 days; MSG was administered through the oral route using an oral gavage

Table 1:

Groups	Treatment	Number of rats per group
A (Control)	Water and feed only	10
B (low dose)	3% LD50, 500 mg of MSG	10
C (Moderate dose)	12% LD50, 2000 mg of MSG	10
D (High dose)	24% LD50, 4000 mg of MSG	10

Animal Sacrifice and Blood Collection: The animals were sacrificed by cervical dislocation 6 hours after the expiration of research. The organs to be worked on was excised following midline abdominal incision. Blood was collected from the retro orbital sinus under mild ether anesthesia, the rat was restrained, the neck gently scuffed and the eye made to bulge. A capillary tube was inserted dorsally in to the eye and blood was allowed to flow by capillary action through the capillary tube into sample bottle. The blood samples were allowed to clot and centrifuged, and the serum was collected to for assay.

Biochemical Essay

Determination of Urea: Blood urea nitrogen (BUN) concentrations was determined by diacetyl monoxime method (Wybenga DR et al.,1971)

Determination of Creatinine: Creatinine concentration was determined by Jaffe method (Bartels and Bolumer,1972.).

Determination of cortisol: The Cortisol immunoassay was done using a cortisol ELISA kit.

Determination of Growth Hormone: Plasma was stored at -20C until assayed for immunoreactive GH e IGF-I. Plasma IGF-I was measured using a commercial RIA after acid ethanol extraction.

Determination of the activity of antioxidant enzymes: In the kidney SOD activity were determined by the method of Sun and Zigman, (1978), CAT activity was determined by the method of Sinha (1972), while GSH activity was determined by the method of Sedlak and Lindsay (1968), and Jollow et al. (1974)

Histological Studies: After careful removal of the testis and prostrate, they were trimmed of fat. They were weighed and immediately fixed in 10% formal saline. After fixing the tissues, they were put into ascending grades of alcohol and then cleared in xylene. They were embedded in paraffin and serial sections of 5µm were obtained. Sections were stained with hematoxylin and eosin. The slides were viewed under light microscope (CELESTRON LCD DIGITAL MICROSCOPE, MODEL 44348) and photomicrographs were taken (200×). Nuclei stained blue black and cytoplasm, pink.

Tissue Processing: Following fixation, the gross anatomy was noted and sections were taken and histologically processed by manual tissue processing method. The tissue processing involves the various stages between fixation and cutting of section (Baker F. J et al, 2004; Ochei J and A. Kolhatkar 2008.)

Staining techniques: Paraffin section after they have been cut was attached to the slides and routine hematoxylin and eosin (H&E) staining method was used (Ochei J and A. Kolhatkar 2008.)

Statistical Analysis: All the values are expressed as mean ± standard error of mean (SEM). Analysis of data was done using GraphPad Prism version 5 for Windows. Differences between groups were analyzed by one-way ANOVA followed by Dunnet post-hoc test. Differences were considered significant when $P < 0.05$

Results

Blood Analysis

Table 2: Evaluation of the toxic effect of monosodium glutamate on blood urea level, creatinine level, cortisol level and growth hormone level in adult male Sprague- Dawley rats.

Biochemical Parameters (mg/dl)	A	B	C	D
Blood Urea	56.00±6.00	50.50±4.50	60.50±3.50	70.00±15.00*
Creatinine	5.50±3.00	4.25±2.65	5.0±2.80	9.13±6.23*
Cortisol	32.68±1.10	50.44±2.51*	52.71±1.76*	18.44±3.79*
Growth Hormone	53.09±11.41	52.71±1.76*	50.44±2.51*	32.81±1.10*

A: Control group, B: 3mg/kg of Monosodium Glutamate (MSG), C: 12mg/kg of Monosodium Glutamate (MSG), D: 24mg/kg of Monosodium Glutamate (MSG). Each value is an expression of mean ± SEM. ($P < 0.05$) * Indicates that values were significant when compared to the control group A

Evaluation of the effect of MSG on the Blood Urea level

Comparing the rats in group D to the control group, it is shown that there is an elevated blood urea level in the rats in group D with the highest dose of monosodium glutamate administered to them.

Evaluation of the effect of MSG on the Creatinine level

The creatinine level of group D has a significant increase when compared with group A (control), B (low dose) and C (moderate dose).

The rats in groups B and C have a significant relatively high cortisol level in comparison with group D.

Evaluation of the effect of MSG on the Growth Hormone level

There was a decrease of growth hormone level of group B, C and D (high dose) compared with group A (control). There is non-significant increase of growth hormone level of group D administered with high dose compared with group A (control).

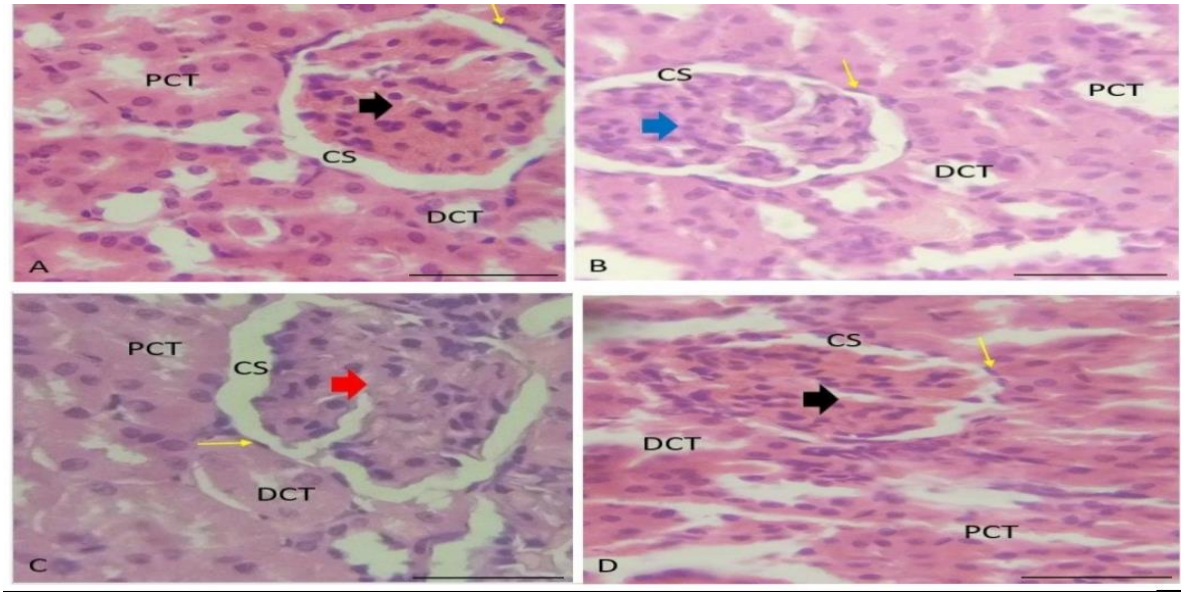

Figure 1:Evaluation of the effect of MSG on the Cortisol level

Table 3: Evaluation of the toxic effect of monosodium glutamate on antioxidant enzyme in adult male Sprague- Dawley rats.

Groups	A	B	C	D
GSH (µmol/ml)	27.32±1.63	35.75±0.31*	22.98±0.80*	31.18±0.80*
SOD (µmol/ml)	3.53±0.19	2.97±0.12*	3.65±0.04*	3.64±0.32*
CAT (µmol/ml)	11.93±0.73	19.80±0.60*	15.74±0.95*	17.55±0.55*
MDA (µmol/ml)	3.59±0.15	2.57±0.40	2.80±0.26	4.40±2.30

A: Control group, B: 3mg/kg of Monosodium Glutamate (MSG), C: 12mg/kg of Monosodium Glutamate (MSG), D: 24mg/kg of Monosodium Glutamate (MSG).

Each value is an expression of mean ± SEM. (P <0.05) * Indicates that values were significant when compared to the control group A

The Superoxide dismutase (SOD) of group B has a non-significant decrease when compared with group A (control group), C, D.

The Glutathione (GSD) of group C has a non- significant decrease if compared with group A (control group), D (high does) and B (moderate does) which has a significant increase.

The catalase of group B, C and D increase significantly compared with group A, while group has the highest significant increase.

The Melondialdehyde (MDA) of group B and C have non-significant decrease compared with group A (control group) and group D (High dose).

Kidney Histology

Effect of the administration of Monosodium Glutamate (MSG) on the kidney histoarchitecture of adult male Sprague Dawley rats.

The photomicrographs that illustrate the histology of the kidney of adult male Sprague Dawley rats of the control group and groups administered with MSG.

The magnification used for these observations is H/EEX400.

Plate 1 Histoarchitecture of the kidney of monosodium glutamate administered adult Sprague- Dawley rats A: normal control, B: 3mg/kg of monosodium glutamate, C: 12mg/kg of monosodium glutamate (P.O), D: 24mg/kg of monosodium glutamate (P.O). H/E X 400. Scale Bar = 120µm

In the control group A, the proximal and distal tubules (PCT & DCT) are well differentiated and organized. The capsular space (CS), glomerulus with podocytes (indicated

by a black thick arrow), and simple squamous epithelial cells (indicated by a yellow thin arrow) are also visible.

In the group B treated with 3mg/kg MSG, the glomerulus with podocytes (indicated by a blue thick arrow) remains well differentiated. However, there is a slight constriction of the capsular space (CS), as well as the proximal and distal convoluted tubules (PCT & DCT) and epithelial cells (indicated by a yellow thin arrow).

In the group C treated with 12mg/kg MSG exhibits constricted proximal and distal tubules (PCT & DCT), along with distorted glomerulus (indicated by a thick red arrow). There is also an irregular and enlarged capsular space (CS), and a thickened and reduced epithelial cell (indicated by a yellow thin arrow).

In the group D treated with 24mg/kg MSG, there is a severe distortion of the glomerulus (indicated by a black thick arrow). The capsular space (CS) appears constricted, and the proximal and distal tubules (PCT & DCT) are degenerated and constricted. Furthermore, there is a loss of epithelial cells (indicated by a yellow thin arrow).

The photomicrograph plate shows the gradual degeneration of the histoarchitecture of the kidneys of adult male Sprague Dawley rats in groups B, C and D in comparison with the kidney histology of the rats in the control group with properly differentiated proximal and distal convoluted tubules, properly defined capsular spaces and glomerulus.

Discussion

The serum urea nitrogen is a measure of renal function. Normally, the serum urea nitrogen level rises in heart failure, dehydration, or a high protein diet and low urea nitrogen level can be seen in liver and renal damage or in liver diseases (W. J. Johnson et al., 1972). With the result showing the rise in urea level of group D (the high dose) compared to the group A, this approves the danger of high consumption of MSG to the heart functions.

The significant increase in creatinine content of the serum following the administration of MSG may be attributed to compromise of the renal functional capacity. MSG might have either interfered with creatinine metabolism leading to increased synthesis or the tissues might have compromised all or part of its functional capacity of tubular excretion (L. Mitchell et al., 1972; J.F. Zilva et al., 1991; Ahamed and R.B. Shabarinath, 2010.). Exposure to MSG may cause an adverse effect on the renal function which might be due to oxidative stress induced by MSG on the renal tissue.

When the hypothalamus is stimulated by chronic stress it may become overstimulated by excessive glutamate in the CSF due to chronic MSG administration. Successively, CRF hypersecretion occurs in the hypothalamus and adaptive down-regulation of the pituitary CRF receptor and decreased ACTH release could follow. As a result, the release of corticosterone, the end product of the HPA axis, may have been decreased. Consequently, it is possible to aggravate the response of the HPA axis by chronic stimulation with excitotoxins such as MSG.This result suggest that HPA axis function can be impaired by overstimulation of the hypothalamus and simultaneous accumulation of excessive glutamate due to chronic MSG administration.

The significant decrease in the growth hormone level of the rats in group D with the highest monosodium glutamate dose establishes that prolonged and increased administration of monosodium glutamate to adult male Sprague Dawley rats hinders the function of growth hormone thus aiding stunted growth.

When newborn (neonatal) rats are given monosodium glutamate (MSG), it affects the hypothalamic arcuate nucleus, which is where growth hormone-releasing hormone is mostly located. Growth hormone release is consequently inhibited.

When neonatal mice are treated with MSG, their hypothalamic arcuate nucleus's growth hormone-releasing hormone neurons are depleted. This lowers the amount of growth hormone in the blood, which in turn inhibits linear growth. These results are in agreement with studies described elsewhere. Neonatal MSG Administration resulted in growth retardation, increased body fat, decreased pituitary Mass (Martin J.B et al., 1978; Tannenbaum G.s and Martin J.B 1976; Terry L.C et al., 1977.).

MSG supplementation either by injection or oral intake has been shown to alter renal antioxidant system markers, including lipid peroxidation byproducts and kidney function in rats (Paul et Al., 2012; Ortiz GG et al., 2005). Paul et al. (2012) found reduced activities of superoxide dismutase, catalase, glutathione-S-transferase and glutathione (GSH) in the kidney after MSG administration. They also reported that markers for lipid peroxidation such as malondialdehyde (MDA) and conjugated dienes were increased in MSG treated renal tissue. It is possible that MSG leads to the excessive production of free radicals and endogenous antioxidants are insufficient to meet the demand. The up-regulation of heat shock cognate 70, an indicator of oxidative stress, and the down-regulation of glutathione-S-transferase in MSG-treated kidneys further strengthens the findings (Paul et al., 2012).

While investigating the effect of MSG consumption on kidney morphology, we observed no significant increase in the kidney sizes of the various experimental groups when compared with the control, but the kidney histology revealed visible renal corpuscle with enlarged glomerulus and interstitial space and tubules with diffused mononuclear cells. Endocapillary hypercellularity is a sign of glomerulonephritis (GN) and when diffuse, it's usually due to post-insults to the kidney. Microscopically, aggregates of lymphocytes, plasma cells, monocytes, and fewer neutrophils are randomly scattered or intensely localized throughout an edematous interstitium. Tubular epithelial cells within severely inflamed areas can be degenerative, necrotic, or both, and profound tubular loss is usually accompanied by eventual replacement fibrosis of the kidney (Melanie & Anthony, 2017), similar results were also reported by Aughey et al; (1984) Kjellstom, (1986), Mitsumari et al; (1995) and Inkielewicz et al; (2003). Bopanna et al; (2009) also studied the changes produced by MSG in rats on atherogenic diet on kidney and liver and showed that there was glomerular mesangial proliferation with extensive damage and vacuolation of tubular epithelial cells and infiltrates of inflammatory cells. Eweka (2007) observed distortion of renal cortical structures with some degree of cellular necrosis due to intake of MSG.

Conclusion

The study shows that, MSG administration elevated the blood urea and creatinine levels of the rats, indicating

impaired renal function and possible kidney damage. MSG administration increased the cortisol levels of the rats, suggesting a dysregulation of the hypothalamic-pituitary-adrenal axis and a heightened stress response. MSG administration decreased the growth hormone levels of the rats, implying a suppression of the hypothalamic arcuate nucleus and a inhibition of linear growth. These results demonstrate that MSG consumption has detrimental effects on the physiological and biochemical parameters of the rats, and may have implications for human health as well. The study contributes to the existing literature on the toxicity of MSG and provides a basis for further research on the mechanisms and consequences of MSG exposure.

Recommendations

1. Read the labels: MSG is a food ingredient; therefore, it would appear in the list of the ingredients which are identified in decreasing order. Also, look for the presence of hydrolyzed vegetable protein or hydrolyzed plant protein. MSG will most likely be found near the bottom of the ingredients list.
2. Use in moderation: MSG does not perk up the flavor of fruit, fruit juice, candy, sweet baked goods, milk and butter. For those foods that benefit from its use, such as vegetable and meat dishes, a general guideline is to allow no more than 5ml (5ml is equivalent to one teaspoon) per kilogram of food or 2ml per six servings of vegetables.
3. Avoid adding MSG to commercially–prepared foods: since many pre- packaged foods already contained MSG, further addition should not be necessary.

References

(1) Tawfik, M.S. and Al-Badr, N. (2012): Adverse Effects of Monosodium Glutamate on Liver and Kidney Functions in Adult Rats and Potential Protective Effect of Vitamins C and E. Food and Nutrition Sciences, 3, 651-659. Thomas M, Sujantha KS, George S.

(2) A. Samuels , " The Toxicity / Safety of MSG: A Study in Suppression of Information , " Accountability in Research , Vol . 6 , No. 4 , 1999 , pp . 259-310 . doi : 10.1080 / 08989629908573933

(3) IFIC , " Review of Monosodium Glutamate , Examining the Myths , " 1994.

(4) K. Ikeda , " On the Taste of the Salt of Glutamic Acid , " Proceedings of 8th International Congress of Applied Chemistry , Vol . 38 , 1917 , p . 147.

(5) FDA , " Food and Drug Administration Background for Monosodium Glutamate , " 1995.

(6) A. Leung and S. Foster , " Encyclopedia of Common Na tural Ingredient Used in Food , " Drugs and Cosmetics , New York , Wiley , 1996 , pp . 373-375.

(7) D. Biodun and A. Biodun , " A Spice or Poison ? Is Monosodium Glutamate Safe for Human Consumption ? " National Concord , 4 January 1993 , p . 5.

(8) R. S. Geha , A. Beiser , C. Ren , R. Patterson , L. C. Gra mmar , A. M. Ditto and K. E. Harris ,. " Review of Allergic Reaction to Monosodium Glutamate and Outcome of a Multicenter Double Blind Placebo - Controlled Study . " Journal of Nutrition , Vol . 130 , 2001 , pp . 1032S - 1038S.

(9) J. U. E. Onakewhor , I. A. O. Oforofuo and S. P. Singh , " Chronic Administration of Monosodium Glutamate In duces Oligozoospermia and Glycogen Accumulation in Wistar Rat Testes , " Africa Journal of Reproductive Health , Vol . 2 , No. 2 , 1998 , pp . 190-197.

(10) I. A. O. Oforofuo , J. U. E. Onakewhor and P. E. Idaewor , " The Effect of Chronic Administration of MSG on the Histology of the Adult Wistar Rat Testes , " Bioscience Research Communications , Vol . 9 , No. 2 , 1997.

(11) P. P. Rogers and J. E. Blundell , " Umani and Appetite : Effects of Monosodium Glutamate on Hunger and Food Intake in Human Subjects , " Physiology and Behavior , Vol . 486 , 1990 , pp . 801-804 . doi : 10.1016 / 0031-9384 (90) 90230-2

(12) L. Stryer , " Biochemistry , " W.H. Freeman and Company , New York , 1995 . [14] A. Guyton and J. Hall , " Textbook of Medical Physio logy , " W. B. Saunders Co. , Philadelphia , 1996.

(13) Wybenga DR, Di Giorgio J, Pileggi VJ (1971) Manual and automatedmethods for urea nitrogen measurement in whole serum. Clin Chem17: 891-895. PubMed: 5571487.

(14) Bartels, H. and Bolumer, M. (1972): Serum creatinine determination without protein
precipitation. Clin. Chem. Acta, 37: 193 – 197. De Groot AP, Feron VJ, Immel H. (1988): Induction of hyperplasia in the bladder epithelium of rats by a dietary excess of acid or base: implications for toxicity/carcinogenicity testing. Food Chem Toxicol 26: 425-434.

(15) Sun M, Zigman S. An improved spectrophotometric assay for superoxide dismutase based on epinephrine autoxidation. Anal Biochem. 1978 Oct;90(1):81–9.

(16) Sinha AK. Colorimetric assay of catalase. Anal Biochem. 1972 Jun;47(2):389–94.

(17) Sedlak J, Lindsay RH. Estimation of total, protein-bound, and nonprotein sulfhydryl groups in tissue with Ellman's reagent. Anal Biochem. 1968;25:192–205.

(18)Jollow DJ, Mitchell JR, Zampaglione N, Gillette JR. Bromobenzene-Induced Liver Necrosis. Protective Role of Glutathione and Evidence for 3,4-Bromobenzene Oxide as the Hepatotoxic Metabolite. Pharmacology. 1974;11(3):151–69.

(19) R. Montgomery , T. Conway and A. Spector , " Bioche mistry : A Case - Oriented Approach , " The C. V. Mosby Company , St. Louis , 1990.

(20) C. Burtis and E. Ashwood , " Tietz Textbook of Clinical Chemistry , " W. B. Saunders Company , London , 1999.

(21)" Merck Manual of Diagnosis and Therapy . " Merck and Co. , Inc. , Rahway , 2004.

(22) Baker, F. J., Silverton, R. E., and Pallister, C. J. (2004): Introduction to Mechanical Laboratory Technology pp 337-384 Seventh Editor.

(23). Ochei J. and A. Kolhatkar (2008): Medical Laboratory Science: theory and practice.
Tata MCGraw-Hill publishing company limited. New Delhi, India.

(24) W. J. Johnson, W. W. Hagge, R. D. Wagoner, R. P. Dinapoli and J. W. Rosevear, "Effects of Urea Loading in Patients with Far-Advanced Renal Failure," Mayo Clinic Proceedings, Vol. 47, No. 1, 1972, pp. 21-29

(25) F. L. Mitchell, N. Veall and R. W. E. Watts, "Renal Function Tests Suitable for Clinical Practice," Annals of Clinical Biochemistry, Vol. 9, 1972, pp. 1-20.

(26) J. F. Zilva, P. R. Panmall and P. D. Mayne, "Clinical

Chemistry in Diagnosis and Treatment," 5th Edition, England Clays Ltd., St. Ives Plc., 1991.
(27) N. A. Vinodini, A. K. Nayanatara, C. Ramaswamy, V. R. Anu, D. K. Rekha, G. K. M. Damadara, B. Ahamed and R. B. Shabarinath, "Study on Evaluation of Monosodium Glutamate Induced Oxidative Damage on Renal Tissue on Adult Wistar Rats," Journal of Chinese Clinical Medicine, Vol. 5, No. 3, 2010, pp. 144-147.
(28) Martin, J. B., Brazeau, P., Tannenbaum, G. S., Willoughby, J. O., Epelbaum, J., Terry, L. C. and Durand, D., Neuroendocrine organization of growth hormone regulation. In S. Reichlin, R.
Baldessarini and J. B. Martin (Eds.), The Hypothalarnus, Iiol. 56, Raven, New York, 1978, pp.
329-357.
(29)Tannenbaum, G. S. and Martin, J. B., Evidence for an endogenous ultradian rhythm governing growth hormone secretion in the rat,
Endocrinology,98 (1976) 540-548.
(30) Terry, L. C., Saunders, A., Audet, J., Willoughby, J. O., Brazeau, P. and Martin, J. B., Physio-
logic secretion of growth hormone and prolactin in male and female rats,
Clin. Endocr., 6 (1977) 195-285.
(31) Terry, L. C. and Martin, J. B., The effects of lateral hypothalamic-medial forebrain stimulation and somatostatin antiserum on pulsatile GH secretion in freely-behaving rats: evidence for a dual regulatory mechanisms, Endocrinology, in press.
(32) Terry, L. C., Epelbaum, J., Brazeau, P. and Martin, J, B., Monosodium glutamate: acute and
chronic effects on growth hormone (GH), prolactin (PRL) and somatostatin (SRIF) in the rat,
Fed. Proc.,
(33) Paul MV, Abhilash M, Varghese MV, Alex M, Nair RH. Protective effects of alpha-tocopherol against oxidative stress related to nephrotoxicity by monosodium glutamate in rats. Toxicol Mech Methods. 2012;22(8):625–30. doi:10.3109/15376516.2012.714008.
(34) Ortiz GG, Bitzer-Quintero OK, Zarate CB, Rodriguez-Reynoso S, Larios-Arceo F, Velazquez-Brizuela IE, et al. Monosodium glutamate-induced damage in liver and kidney: a morphological and biochemical approach.BiomedPharmacother.2006;60(2):86–91. doi:10.1016/j.biopha.2005.07.012.
(35) Sharma A, Wongkham C, Prasongwattana V, Boonnate P, Thanan R, Reungjui S, et al. Proteomic analysis of kidney in rats chronically exposed to monosodium glutamate. PLoS One. 2014;9(12):e116233. doi:10.1371/journal.pone.0116233.
(a)Melanie A. Breshears and Anthony W. Confer. (2017): Pathologic Basis of Veterinary Disease. 617–681.
(36) Aughey E, Feli GS, Scott R, Black M. (1984): Histopathology of early effects of oral cadmium in the rat kidney.Environ Health Perspect. ; 54:153–161
(37) Kjellstrom T. (1986): Renal effects. In: Friberg L, Elinder CG, Kjellstrom T, Norgderg GF, eds. Cadmium and Health: A Toxicology and Epidemiological Appraisal. Tawfik, M.S. and Al-Badr, 2. Boca Raton: CRC Press; :21--109 .
(38) Mitsumari K, Shibutani S, Sato S, (1998). Relationship between the development of hepatorenal toxicity and cadmium accumulation in arts. Arch Toxicol. 72:545–552.
(39) Inkielewicz I, Krechniak J. (2003): Fluoride content in soft tissues and urine of rats exposed to sodium fluoride in drinking water. Fluoride Clin Chem.; 36(4):263–266 Ikeda. K. (2002).
(40) Bopanna KN, Balaraman R, Nadig RS. (1999): Organotropic ultrastructural changes produced by monosodium glutamate in rats on athrogenic diet: Effect of S-Allyl Cysteine sulphoxide. Ind J Pharmacol. ; 31:266–274.
(41) Eweka AO. (2007: Histological studies of the effects of monosodium glutamate of the kidney of adult Wistar rats. Internet J Health. ; 6(2):