IOSR Journal of Environmental Science, Toxicology and Food Technology (IOSR-JESTFT)
e-ISSN: 2319-2402,p- ISSN: 2319-2399.Volume 13, Issue 3 Ser. III (March. 2019), PP 56-62
www.iosrjournals.org

Aspartame and Monosodium Glutamate Disturb Antioxidant Status of Male Albino Rat

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Abstract:*The objective of the present study is to evaluate the effect of food additives as aspartame (ASP) and monosodium glutamate (MSG) either individually or in combination on antioxidant parameters of adult male albino rats. Superoxide dismutase (SOD) and catalase (CAT) activitiesintheliverwere significantly increased in rats of the most treatedgroupsofthe tested food additives. Malonaldehyde (MDA) and glutathione (GSH) contents in the liver showed significant reduction in MSG,ASP+MSGand ASP treatedgroupscompared to the control, respectively.The lone administration of ASP and MSG induced marked decrease in the kidney MDA content, compared to the control group. ThekidneyGSH content was significantly decreased only in ASP+MSG treated group compared to control.The kidney CAT activitywas significantly increased in case of rats given mixture of ASP and MSG, while it was not affected in the rest of groups. Positive significant correlation coefficient (r= 0.908) between kidney CAT and MDA was observed only for ASP treated group. BrainSOD, CAT and MDA and kidney SOD levels were not varied statistically from the control due to food additives consumption. On contrary,the brain SOD activity was significantly inhibited from the control after treatmentwith MSG. Therefore, the consumption of the tested food additives induced harmful changes in the antioxidant status of the rat. So, its consumption should be restricted.*

Keywords*:Aspartame, Monosodium Glutamate, Antioxidant parameters.*

Date of Submission: 24-03-2019 Date of acceptance: 08-04-2019

I. Introduction

Food additives are used to improve food quality such as color, taste or appearance (Duffy 2002;Chaudhary 2010).Aspartame is one of food additive that most widely used as sweeteners, discovered in 1965, it is produced commercially from two amino acids, L-aspartic and L-phenyl alanine (Wardlaw and Kessel2002).It is permittedin Egypt since 1981 (Ismail and El-Gabry1996 ;Abdallah 2002).However, food and drug administration (FDA) presented a warning label regarding the potential toxicity of aspartame in patients with phenylketonuria and liver diseases (Duffy 2002). The accepted daily intake recommended by the FDA is 50mg/kg body weight/day (Leon et al. 1989).

Monosodium Glutamate (MSG), is the sodium salt of naturally occurring non-essential amino acid L-form of glutamic acid, constitutes about 20% of total amino acids found in natural protein source (Gehaet al. 2000). MSG is one of the world's most extensively used food additives, which is ingested as part of commercially processed food (Husarova and Ostalmikova 2013).MSG serves as an energy source for certain tissues and as a substrate for glutathione synthesis. Excessive consumption of MSG may cause many symptoms as brain damaging potential, stunted skeletal development, behavioral aberration, neuro-endocrine disorders, and hyperglycemia (Gehaet al. 2000).

The oxidative stress elicited by aerobic metabolism, is a generator for animal and human cells to develop a pervasive antioxidant defense system, which consists of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase together with a number of low molecular-weight antioxidants such as ascorbate, α-tocopherol and glutathione (GSH), cysteine, thioredoxin, vitamins, etc. (Fridovich 1997; Halliwell and Gutteridge 1999). Abhilashet al. (2011) showed that the activity of reduced glutathione (GSH) was significantly reduced in the liver of rats received aspartame, but no significant changes were observed in (SOD) and catalase (CAT) activity.On the other handMourad (2011) found that daily oral administration of ASP (40 mg/kg) for 6 weeks induced oxidative stress in the liver and kidney of male albino rats with concomitant increased SOD activity and reduced GSH content in the liver tissue. Prokicet al.

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(2015)reported that chronic ASP administration to rats, caused enhancement in the concentration of reduced GSH and the activity of CAT, which is an indication of oxidative stress in erythrocytes. It also induced a significant increase in the activity of SOD, glutathione peroxidase levels (GPx), and CAT activity (Ashoket al. 2015).While Saleh (2015)andFinamoret al. (2017)found that there was a decrease in GSH levels induced by long-term consumption of the artificial sweetener. Lebdaet al. (2017)found that rats treated with ASP showed significant increase in the hepatic MDA concentration, significant decrease, in the hepatic GSH concentration, CAT and SOD in rats that received ASP, compared to control.

El-Sabaghetal. (2014) showed that there are pathological changes in the brain of rat increased from mild to severe by increasing the concentration of MSG which led to damage of the brain cells. Abdel-Reheimet al. (2014) found that there is a decrease in CAT, GSH, and SOD in liver and kidney of MSG treated rats. Some investigators reported that ingestion of MSG induced oxidative stress and halt the antioxidant defense(Okwudiriet al. 2012; Abdel-Reheimet al. 2014; El-Sabaghetal. 2014; Ashok et al. 2015;Tawfeket al. 2015).

The available data exploring the antioxidant defense of rat given ASP and MSG at or below the acceptable daily intake is insufficient. Furthermore, that of their combination is unavailable. Therefore, the present work was carried.

II. Materials and Methods

1. Experimental Animals:

The present study was carried out on adult male albino rats, (weighing 120±10g). The animals were obtained from Helwan Farm of Egyptian Organization for Vaccine and Biological Preparations. They were acclimatized for 10 days in well-ventilated room under controlled laboratory conditions. After that, rats were randomly divided into 4 experimental groups (5 in each) and supplied with diet and water *ad libitum*. Animals were handled in the laboratory following the standard principles of laboratory animal care (NIH 1985)

2. Experimental groups and tissue sampling: -

Group I (control group): rats in this group received a daily oral dose of 1ml of distilled water for one month.

Group II (ASP treated group): rats in this group received a daily oral dose of ASP 0.13 g (dissolved in 1ml of distilled water) per kg of body weight for one month.

Group III (MSG treated group): rats in this group received a daily oral dose of MSG 0.13 g (dissolved in 1ml of distilled water) per kg of body weight for one month.

Group IV (ASP+MSG treated group): rats in this group received a daily oral administration of ASP 0.13 g + MSG 0.13 g (dissolved in 1ml distilled water) per kg of body weight for one month.

The examined food additives structure and sources were described earlier in El-Ezabyet al. (2018).At the end of the experimental period, rats were fasted overnight. The animals of each group were anaesthetized by ether inhalation and then blood samples were collected in dry glass tube using a syringe. Serum was separated by centrifugation at 3000 rpm for 15 min, and thenit was stored at -20 °C until analysis.

3. Determination of antioxidant parameters:

Liver, kidneys and brain were removed from dissected rats. Two hundred and fifty mg of each tissue was kept in 1 ml of phosphate buffer saline (PBS) and homogenized by using homogenizer, then centrifuged by using cooling centrifuge (at -4°C, and 10000 rpm), then supernatant was removed for antioxidant parameters determination.

Determination of superoxide dismutase (SOD, U/g) activity was determined according to Nishikimiet al. (1972) by using SOD Biodiagnostik and Research Reagent Colorimetric Method Assay Kit.Determination of reduced glutathione (GSH, mg / tissue) content was determined according to Beutleret al. (1963), using GSH Biodiagnostik and Research Reagent Colorimetric Method Assay Kit.Determination of catalase (CAT, U / g) activity was determined according to Aebi (1984) using CAT Biodiagnostik and Research Reagent Colorimetric Method Assay Kit.Determination of Lipid Peroxide Malondialdehyde (MDA, nmol / g fresh tissue) activity was determined according to Ohkawaet al. (1979) using MDA Biodiagnostik and Research Reagent Colorimetric Method Assay Kit.

5. Statistical analysis

The data expressed as mean ± SE.It was analyzed using analysis of variance (ANOVA) followed by Duncan's multiple range test (Duncan 1957).Pearson correlation coefficient was computed between every two parameters. Differences were considered significant at $P \leq 0.05$. All statistical analysis was done using SPSS software version (V20)

III. Results

3.1.Antioxidant parameters in liver

Rats treated with either ASP or MSG showed significant increase in liver SOD activity and non-significant increase for their combination compared to control table (1). Treatment with ASP showed non-significant decrease in liverMDAlevel, but treatment with MSG and the mixture of ASP+MSG showed significant decreases in its content compared to control. Treatment with ASP showed significant decrease in GSH content compared to control and non-significant differences in other treated groups. The data of CAT activity in the liver showed that all treated groups have significant enhancement over the control value(table 1). The data tabulated in table (2) showed no correlation between the tested parameters in the liver tissue.

3.2.Antioxidant parameters in the kidney

The data of antioxidant parameters in the kidney of rats exposed for one-month to oral administration of the examined food additives were presented in table (3). For SOD activity in the kidney, all treatments induced non-significant changes from the control. ASP and MSG treated groups exhibited significant decrease in MDA content (maximum difference was -47.14% from the control) while the ASP+MSG combinations have non-significant decrease. Treatment with either ASP or MSG caused non-significant decrease for GSH content. Compared to control group, significant decrease in its content was recorded for ASP+MSG treated group. Catalase activity (CAT) was not obviously affected in rats given ASP or ASP+MSG. While the treatment with MSG showed significant rise of CAT (being 172.96% over the control value (table 3). Worthy to mention that kidney CAT × MDA was high proportionally correlated (r = 0.908) for ASP treated rat.The rest of parameters showed non-significant correlation (table 4).

3.3. 3.Antioxidant parameters in the Brain

Brain SOD, CAT activities and MDA contentshowed that treatment withthetested food additives caused non-significant fluctuations compared to control, table (5). But rats treated with MSG showed significant decreased values in the tested parameters compared to control and other treated groups. The data highlights that all treated groups (ASP, MSG and ASP+MSG) showed significant increase in GSH content compared to control. Its maximal increase was recorded for MSG treated group (table 5), being 128.09% over the control value. Pearson correlation coefficient presented in table (6) showed weak correlation between all the tested parameters for all tested groups.

IV. Discussion

The animals during their life exposed to various stressors. Some of them generate free radicals, reactive oxygen species (ROS). In order to prevent the potential effects of ROS, organisms have evolved multiple systems of antioxidant defense including both enzymatic and non-enzymatic strategy, and are essential for the cellular metabolism and function (Mates 2000).

In regards to the control, the present study revealed significant increase in SOD and CAT activities in the liver for rats treated with the examined food additives. The increased CAT activity recorded for MSG may be an indication of oxidative stress(Tawfeket al. 2015). On the other side, the liver reduced GSH and MDA contents showed significant reduction for rats treated with ASP and MSG and their combination, compared to the control, respectively. The reduction of antioxidant metabolites (GSH and MDA) in rat as an effect of food additives was previously recorded (Anwar and Mohamed 2010; Abdel-Reheimet al. 2014;Finamoret al. 2017).In contrast, enhanced MDA was reported for rat given food additives (Tawfeket al. 2015).Lipid peroxidation is a major indicator of oxidative damage initiated by ROS and causes impairment of membrane function (Selvakumaret al. 2006). It was explained that MDA level is increased as a product of lipid peroxidation occurred by ROS action on lipids of cellular membrane (Amin et al. 2010). The disturbed oxidative stress biomarkers in the liver tissue reported in the present study are an indication of liver impairment.

Although some information is available on the aspartame induced toxicity at various levels (Christian et al. 2004;Simintziet al. 2007), the studies on the effect of long-term oral exposure of aspartame on liver antioxidants are insufficient. Moreover, most of studies on aspartame have been carried out to understand the mechanisms of neurotoxicity (Christian et al. 2004;Tsakiriset al. 2006;Simintziet al.2007; Bergstrom et al. 2007) and cancer (Soffritti et al. 2006; Gallus et al. 2007). Aspartame-induced liver inflammation and necrosis is associated with GSH depletion and a decrease in glutathione peroxidase and glutathione reductase activities (Abhilashet al. 2011). Aspartame also provokes adrenal cell apoptosis *in vitro*(Horioet al. 2014) and brain apoptosis *in vivo*(Ashok and Sheeladevi 2014).

Hence, GSH depletion and changes in GSH-related enzymes are considered main features linked to aspartame-induced oxidative stress and injury (Finamoret al. 2014; Ashok and Sheeladevi 2014;Prokic et al. 2015). Moreover, methanol may cause oxidative stress and is considered the major contributor to ASP toxicity upon administration (Abdel-Salam et al. 2012;Finamoret al.2014 ;Choudhary and Devi

2016).Subchronicconsumption of aspartame significantly increased lipid peroxidation products in the brain, liver, and kidneys with a concomitant depletion of enzymatic (GST, GPx, SOD, and CAT) and non-enzymatic (GSH) antioxidant levels (Adaramoye and Akanni 2016). This finding was consistent with the result of the present study, explaining another mechanism of hepatic damage induced by aspartame other than lipid alterations. Alwaleedi(2016) reported that a 60-day aspartame treatment significantly increased lipid peroxidation with a remarkable reduction in antioxidant status in the liver and kidney tissues of rats. Aspartame-induced oxidative stress may be attributed to its methanol content, a hallmark of aspartame toxicity (Parthasarathyet al. 2006; Castro et al. 2002), and the free radicals produced during aspartame metabolism that cause lipid peroxidation and depletion of antioxidant enzymes (Adaramoye and Akanni 2016).

The present study recorded elevated activities of SOD and CAT in kidney of rat treated with the tested food additives. Similar results were reported by Tawfeket al. (2015).Also, the recorded data highlighted reduction in renal MDA and GSH, which are an indication of renal oxidative damage induced by food additives. Such harmful effect was previously recorded by Tawfik and Al-Badr (2012). The extent of oxidative stress-induced damage depends not only on the nature and amount of ROS involved but also on the duration of ROS exposure and ROS scavengers (El-Tohamy 2012).

The recorded data in the present undertaken indicated significant reduction of brain SOD activity for rat treated with MSG compared to the control. The brain GSH content showed significant increase in all treated groups compared to the control. These significant changes of the antioxidant biomarkers reflect the generation of the oxidative stress in the brain. This is in agreement with those reported by Ashok *et al.* (2015) for ASP.

Oxidative stress is the general phenomenon of oxidant exposure and antioxidant depletion, or oxidant-antioxidant balance (Bidlack and Lancaster 1998). The central nervous system is vulnerable to free radical damage because of brain′s high oxygen consumption, its abundant lipid content, and the relative paucity of antioxidant enzymes as compared with other tissues. Tawfeket al. (2015)foundthatsignificant increase in MDA and lipid peroxidation could also be due to the increases in the blood glutamate and glutamine, which are reported to favor lipogenesis. Glutamate is poorly transported across cell membranes and could accumulate intracellular, altering the redox state of the cell. In this altered redox state, the cell favors lipid synthesis and tends to shut down lipolysis. The increased level of glutamate increases the concentration of glutamine, which may cause toxicity in various organs of body, especially brain.

V. Conclusion

The present study concluded that administration of ASP and MSG either individually or in combination caused oxidative stress and weekend the antioxidant potentiality of rat body. It also explores the potentiality of the ASP and MSG mixture to induce interactive toxicity. So, the present study recommend staying away from using MSG and ASP in our foods.

Conflict of Interest: The authors declare that no conflict of interest related to this article.

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Table (1): Antioxidant parameters in liver tissue (Superoxide dismutase activity, SOD U/gm, malonealdahide content, MDA nmol/g, glutathione content, GSH mg/g, catalase activity, CAT U/g) of male albino rats orally administered with aspartame (0.13 g/Kg b.w.), monosodium glutamate (0.13 g/Kg b.w.) and their combination (Monosodium glutamate + Aspartame 0.13 g/Kg b.w. for each) for one month.

Groups / Parameters		Control	Aspartame (ASP)	Monosodium glutamate (MSG)	ASP + MSG
SOD (U/g)	Mean± SE	1086.20±68.96 ^{c}	1427.41 ±22.47 ^{a}	1332.59± 17.88 ^{ab}	1224.13± 68.96 ^{bc}
	% Of Change	-	31.41%	22.68%	12.69%
MDA (nmol/g)	Mean± SE	533.04 ± 76.83 ^{a}	399.59 ± 26.07 ^{ab}	275.35 ± 44.50 ^{b}	317.42 ± 23.81 ^{b}
	% Of Change	-	-25.03%	-48.34%	-40.45%
GSH (mg/g)	Mean± SE	56.61 ± 7.16 ^{a}	16.21 ± 1.71 ^{b}	50.46 ± 2.35 ^{a}	58.60 ± 3 ^{a}
	% Of Change	-	-71.36%	-10.86%	3.51%
CAT (U/g)	Mean± SE	35.28 ± 4.12 ^{b}	292.13 ± 25.72 ^{a}	231.59 ± 73.08 ^{a}	272.05 ± 8.82 ^{a}
	% Of Change	-	728.03%	556.43%	671.11%

Number of animals in each group =5. In the same row:
Data were presented as mean ±SE. Similar letters mean non-significant difference.
% of change = {(Value of treated – Value of control) / Value of control} X 100

Table (2): Correlation coefficient of the tested antioxidant parameters in the liver of different groups.

Groups / Parameters	Control	ASP	MSG	ASP+MSG
SOD × CAT	0.517	-0.839	-0.672	-0.848
SOD × GSH	0.218	0.152	0.241	-0.200
SOD × MDA	-0.568	0.462	-0.169	0.118
CAT × GSH	-0.232	-0.152	0.028	0.393
CAT × MDA	-0.327	-0.220	0.123	-0.344
MDA × GSH	0.093	0.735	0.801	-0.454

Significant at P <0.05

Table (3): Antioxidant parameters in kidney tissue (Superoxide dismutase activity, SOD U/gm, malonealdahide content, MDA nmol/g, glutathione content, GSH mg/g, catalase activity, CAT U/g) of male albino rats orally administered with aspartame (0.13 g/Kg b.w.), monosodium glutamate (0.13 g/Kg b.w.) and their combination (Monosodium glutamate + Aspartame 0.13 g/Kg b.w. for each) for one month.

Groups / Parameters		Control	Aspartame (ASP)	Monosodium glutamate (MSG)	ASP + MSG
SOD (U/gm)	Mean± SE	1279.31± 40.21 ^{a}	1385.34±78.04 ^{a}	1316.09± 22.99 ^{a}	1224.13 ±68.96 ^{a}
	% Of Change	-	8.28%	2.87%	-4.31%
MDA nmol/gm)	Mean± SE	357.26 ± 36.62 ^{a}	231.58 ± 40.53 ^{b}	188.71± 25.02 ^{b}	249.70 ± 30.42 ^{ab}
	% Of Change	-	-35.17%	-47.17%	-30.10%
GSH mg/tissue	Mean± SE	72.95 ± 3.07 ^{a}	69.11 ± 1.75 ^{a}	60.05 ± 3.69 ^{ab}	43.29 ± 11.90 ^{b}
	% Of Change	-	-5.26%	-17.68%	-40.65%
CAT (U/gm)	Mean± SE	77.30 ± 13.23 ^{b}	64.23 ± 6.09 ^{b}	211 ± 30.86 ^{a}	109.56 ± 21.30 ^{b}
	% Of Change	-	-16.90%	172.96%	41.733%

Number of animals in each group =5. In the same row:
Data were presented as mean ±SE. Similar letters mean non-significant difference.
% Of change = {(Value of treated – Value of control) / Value of control} X 100

Table (4): Correlation coefficient of the tested antioxidant parameters in kidney of different groups.

Groups / Parameters	Control	ASP	MSG	ASP+MSG
SOD × CAT	-0.117	0.712	-0.848	0.421
SOD × GSH	0.072	-0.437	0.276	0.426
SOD × MDA	0.109	0.548	0.027	-0.220
CAT × GSH	-0.727	-0.143	-0.640	0.253
CAT × MDA	-0.196	0.908*	-0.046	-0.737
MDA × GSH	-0.529	0.204	-0.259	-0.526

Significant at P <0.05

Table (5): Antioxidant parameters in brain tissue (Superoxide dismutase activity, SOD U/gm, malonealdahide content, MDA nmol/g, glutathione content, GSH mg/g, catalase activity, CAT U/g) of male albino rats orally administered with aspartame (0.13 g/Kg b.w.), monosodium glutamate (0.13 g/Kg b.w.) and their combination (Monosodium glutamate + Aspartame 0.13 g/Kg b.w. for each) for one month.

Group / Parameter		Control	Aspartame (ASP)	Monosodium glutamate (MSG)	ASP + MSG
SOD (U/gm)	Mean± SE	1486.20 ± 42.14ª	1537.58±57.98ª	1293.10 ± 39.81 ᵇ	1477.01±45.98ª
	% Of Change	-	3.45%	-12.99%	0.61%
MDA nmol/gm	Mean± SE	208.07 ± 28.26ª	262.89 ± 13.82ª	273.56 ± 41.85ª	232.35 ± 21.38ª
	% Of Change	-	26.34%	31.47%	11.66%
GSH mg/tissue	Mean± SE	27.12 ± 6.53 ᵇ	57.50 ± 3.74ª	61.86 ± 4.96ª	60.31 ± 6.08ª
	% Of Change	-	112.02%	128.09%	122.38%
CAT (U/gm)	Mean± SE	201.57 ± 22.29ª	220.05 ± 20.29ª	209.90 ± 9.43ª	259.98 ± 16.56ª
	% Of Change	-	9.16%	4.13%	28.97%

Number of animals in each group =5. In the same row:
Data were presented as mean ±SE. Similar letters mean non-significant difference.
% of change = {(Value of treated – Value of control) / Value of control} X 100

Table (6): Correlation coefficient of the tested antioxidant parameters in brain of different groups.

Groups / Parameters	Control	ASP	MSG	ASP+MSG
SOD × CAT	0.438	0.516	0.349	0.090
SOD × GSH	0.246	-0.100	0.603	0.742
SOD × MDA	-0.457	0.350	-0.787	-0.652
CAT × GSH	-0.698	-0.510	0.671	-0.524
CAT × MDA	0.300	-0.492	-0.844	-0.004
MDA × GSH	-0.553	0.509	-0.717	-0.739

Significant at P <0.05