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Original article

Ivermectin Protects against Monosodium Glutamate-Induced Excitotoxicity in the Rat

Rotimi O. Arise[1], Abimbola K. Arise[2], Oluwole I. Oyewole[3], Sylvia O. Malomo[1]

[1]*Department of Biochemistry, University of Ilorin, Ilorin, Nigeria*
[2]*Department of Home Economics and Food Science, University of Ilorin, Ilorin, Nigeria*
[3]*Biochemistry Unit, Department of Chemical Sciences, Osun State University Osogbo, Nigeria*

SUMMARY

Monosodium glutamate (MSG), an established excitotoxic food additive, has been found to induce oxidative stress in all tissues. To examine the protective effects of ivermectin on MSG-induced excitotoxicity, 28 male albino rats were randomized into four groups. Group 1, the control, received 1 ml of oral distilled water, group 2 was administered an aqueous solution of MSG (4 mg/kg body weight/day). Group 3 was co-administered with the same dose of MSG and 0.4 mg/kg body weight of ivermectin, while group 4 rats received orally the same dose of MSG for 2 weeks, after which ivermectin was administered orally for 1 week. Administration of MSG orally for 21 days and for 14 days, followed by oral administration of ivermectin for 7 days, significantly increased ($p < 0.05$) glutathione-S-transferase, nitric oxide synthase, superoxide dismutase and catalase activities as well as malondialdehyde and intracellular Ca^{2+} concentrations while Na^{+} - K^{+} - ATPase, Ca^{2+} - Mg^{2+} - ATPase, acid phosphatase (ACP) and alkaline phosphatase (ALP) activities were significantly reduced ($p < 0.05$) compared to the control. However, co-administration of MSG and ivermectin for 21 days did not show any significant difference ($p > 0.05$) in all the parameters studied compared to the control. This result suggests that ivermectin may protect against MSG-induced excitotoxicity in rats.

Key words: **monosodium glutamate, ivermectin, excitotoxicity, oxidative stress, glutamate channels**

Corresponding author:
Rotimi O. Arise
Email: arise.ro@unilorin.edu.ng

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INTRODUCTION

It is known that under normal physiological conditions, an effective Ca^{2+} buffered system occurs after the neurotransmitter-mediated opening of glutamate, N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) receptor channels, and voltage-dependent Ca^{2+} channels that maintain the intracellular Ca^{2+} concentration in response to glutamate release (1, 2). Many chemicals have demonstrated that they possess the ability to disrupt this buffer system, resulting in increased postsynaptic calcium levels, producing toxic effects on neurons and other excitable tissues (3).

Excitotoxicity is a pathological process that can lead to the damage and destruction of nerve cells due to hyperstimulation of neurotransmitters such as glutamate and other similar substances. This process takes place when the excitatory neurotransmitter receptors, glutamates (glutamate receptors), such as the NMDA receptor and the AMPA receptor, become over-activated. One of these chemicals is monosodium glutamate (MSG). MSG is an additive in food that is widely used as a flavor enhancer. It is found in significant amounts in processed foods and has a chemical composition similar to that of neurotransmitters of brain glutamate. This amino acid can act on several types of receptors. The receptors are divided into two major groups: ionotropic glutamate receptors (iGluR) and metatropic glutamate receptors (mGluR) (4). MSG is an established neuro- and excitotoxin (5, 6).

During the first week of newborn rats, the administration of MSG to newborn rats induces a neurodegenerative process, characterized by many neurochemical alterations of surviving neurons in the brain (7). Although the mechanism of action of MSG as an excitotoxin still remains unclear, however, Bojanić et al. (8) hypothesized that neural membrane permeability for calcium could be altered by high concentration of MSG.

Many glutamate receptor antagonist compounds such as diltiazem and some macrolide antibiotics have demonstrated a protective effect against MSG toxicity when co-administered to rats (8). Ivermectin (22, 23-dihydroavermectin B1a), a member of the macrocyclic lactones (macrolides) avermectin class isolated from *Streptomyces avermitilis*, is a potent antihelminthic agent used to treat onchocerciasis (river blindness) (9) and lymphatic filariasis (elephantiasis) (10) in humans. It appears as either white or yellowish-white powder with a melting point of 156 °C. It is easily soluble in methanol and each tablet contains cellulose, pre-crystallized starch, magnesium, butylated hydroxyanisole, and citrate powder.

As a macrocyclic lactone, ivermectin produces a flaccid paralysis of somatic worm musculature and inhibits parasite feeding by blocking pharyngeal pumping (11), suggesting that a disturbance of ingestion is the main action of this compound. The half-maximal effecttive concentration (EC50) for the biological activity of ivermectin is strongly correlated with their ability to activate glutamate-sensitive channels and their binding affinity for membrane preparations of nematodes (12). Ivermectin induces the release of Ca^{2+} from reticulum of the sarcoplasm (13). This may be due in part to the activation of glutamate-sensitive channels via ryanodine (RyR) Ca^{2+} receptor channels in excitable tissues. An interesting observation is the ability of macrolide antibiotics to exert a protective effect against glutamate excitotoxicity (14). This protective potential may depend on the structure, with larger nucleus macrolides being more effective (15).

However, there is a dearth of information regarding the potential of compounds that are not antibacterial but possess the macrocyclic core structure to exhibit such a protective property. To this end, we assessed the protection potential of ivermectin against excitotoxicity induced by monosodium glutamate in rats.

MATERIAL AND METHODS

Chemicals

The AMP-buffered sodium thymolphthalein monophosphate substrate used for ALP was a product of Teco Diagnostics, Lakeview Avenue, Anaheim, Canada. Ivermectin and monosodium glutamate were the products of Merck and Co. England and Ajinomoto, Chicago, respectively. All other reagents used were of analytical grade, purchased from Merck and Co. England and were prepared in all-glass distilled water. The reagents were stored in clean and sealed reagent bottles.

Experimental animals

An aggregate of 28 female *Rattus novergicus* (albino rats) of average weight 169.32 g ± 5.22 g were obtained from the Animal Conservation Unit of the Department of Biochemistry, University of Ilorin, Ilorin, Kwara State, Nigeria. The animals were kept in plastic cages under standard laboratory conditions and had free access to rat granules and tap water *ad libitum*. The studies

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are in accordance with the Principles of Animal Care (16).

Experimental design

The rats were randomly grouped into four groups and each group comprised seven rats. Group 1 served as a control and received 1 ml of oral distilled water. Group 2 received orally an aqueous solution of MSG (4 mg / kg body weight / day). Group 3 received concomitant administration of 4 mg / kg body weight of MSG and 0.4 mg / kg body weight of ivermectin (IVER), while group 4 rats received 4 mg / kg body weight of MSG orally for 2 weeks after which ivermectin (0.4 mg/kg body weight) was orally administered for 1 week. The treatments lasted 21 days and the rats were sacrificed by decapitation 24 hours after the last administration. The brain was collected and perfused in normal saline, after which tissue homogenate was prepared.

Biochemical analysis

The activity of acid phosphatase (ACP) was analyzed by adopting the method of Armstrong (17). The method of Bassey et al. (18) with slight modification as described by Wright and Plummer (19) was used to assay for alkaline phosphatase (ALP) activity. ATPase activities were determined using the method of Ronner et al. (20) as modified by Bewaji et al. (21) and catalase (CAT) by the method of Sinha (22). The method described by Varshney and Kale (23) was employed to determine the concentration of malondialdehyde (MDA). The activities of glutathione-S-transferase (GST), nitric oxide synthase (NiOS) and superoxide dismutase (SOD) were analyzed by adopting the procedure of Habig et al. (24), Bredt et al. (25) and Oyanagui (26), respectively. Reduced glutathione (GSH) and calcium ion concentration were obtained by the method of Moron et al. (27) and Chu et al. (28), respectively.

Statistical analysis

Comparisons among groups were carried out using a Duncan's multiple range test (29) and values were considered to be significant at $p < 0.05$.

RESULTS

Co-administration of MSG and ivermectin for 21 days in rats revealed no significant difference ($p > 0.05$) in brain GSH and MDA concentrations and in GST activity compared to control. However, the administration of MSG alone for 21 days and 14 days, followed by the administration of ivermectin for 7 days, resulted in a significant ($p < 0.05$) decrease in the level of these parameters compared with the control (Table 1).

There was a significant ($p < 0.05$) increase in calcium ion concentration in the brains of MSG-treated rats alone and those administered MSG and ivermectin compared to the control group, but the co-administered groups with MSG and ivermectin did not show any significant difference ($p > 0.05$) compared to the control. In addition, the activities of Na^+ - K^+ and Ca^{2+} - Mg^{2+} ATPases in the brain tissues of group 2 rats (MSG alone for 21 days) and group 4 (MSG for 14 days and ivermectin for 7 days) were significantly increased while co-administration of both chemicals showed no significant change ($p > 0.05$) (Table 2).

Table 1. **The effect of administration of monosodium glutamate (MSG) and ivermectin (IVER) on reduced glutathione (GSH), glutathione S-transferase (GST) activity and malondialdehyde formation in rat brain**

Groups	GSH $\mu g\ g^{-1}$ protein	GST nmol $min^{-1}\ mg^{-1}$ protein	MDA nmol mg^{-1} protein
Control	1.70 ± 0.11[a]	72.51 ± 1.86[a]	0.61 ± 0.04[a]
MSG	0.55 ± 0.03[b]	111.94 ± 7.50[b]	9.57 ± 0.55[b]
MSG+IVER	1.91 ± 0.12[a]	74.37 ± 4.30[a]	0.74 ± 0.03[a]
IVER after MSG	0.49 ± 0.02[b]	114.37 ± 9.82[b]	10.00 ± 0.90[b]

Values are mean (n = 7) ± SEM. Values with different alphabets in each column are significantly different at $^*p < 0.05$

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Table 2. **The effect of administration of monosodium glutamate (MSG) and ivermectin (IVER) on Ca^{2+} level, Na^{+} - K^{+} and Ca^{2+} - Mg^{2+} ATPase activities in rat brain**

Groups	Ca^{2+} mg 100 ml^{-1}g wet $weight^{-1}$	Na^{+}- K^{+} ATPase µmol mg^{-1} protein hr^{-1}	Ca^{2+}- Mg^{2+} ATPase µmol mg^{-1} protein hr^{-1}
Control	8.12 ± 0.71[a]	0.47 ± 0.02[a]	1.21 ± 0.11[a]
MSG	19.57 ± 1.10[b]	0.16 ± 0.01[b]	0.97 ± 0.07[b]
MSG+IVER	7.07 ± 0.41[a]	0.51 ± 0.03[a]	1.19 ± 0.10[a]
IVER after MSG	17.97 ± 1.52[b]	0.18 ± 0.01[b]	0.99 ± 0.07[b]

Values are mean (n = 7) ± SEM. Values with different alphabets in each column are significantly different at $^{*}p < 0.05$

The brain activity of superoxide dismutase (SOD), nitric oxide synthase (NiOS) and catalase of rats in groups 2 and 4 increased significantly ($p < 0.05$), while rats co-administered with MSG and ivermectin (group 3) showed no significant difference ($p > 0.05$) when compared to the control as represented in Table 3.

The effect of administration of monosodium glutamate (MSG) and ivermectin (IVER) on the activities of acid phosphatase (ACP) and alkaline phosphatase (ALP) in rat brain tissue as presented in Table 4 has a similar pattern to the results presented in Table 1.

Table 3. **The effect of administration of monosodium glutamate (MSG) and ivermectin (IVER) on the activities of nitric oxide synthase (NiOS), superoxide dismutase (SOD) and catalase (CAT) in rat brain**

Groups	NiOS °Unit mg^{-1} protein	SOD µmol min^{-1} mg^{-1} protein	CAT µmol min^{-1} mg^{-1} protein
Control	94.11 ± 7.40[a]	1001.32 ± 61.42[a]	0.35 ± 0.01[a]
MSG	122.48 ± 10.11[b]	1189.24 ± 65.91[b]	2.33 ± 0.10[b]
MSG+IVER	90.41 ± 6.50[a]	998.17 ± 21.66[a]	0.29 ± 0.02[a]
IVER after MSG	121.12 ± 11.14[b]	1178.15 ± 71.70[b]	2.21 ± 0.19[b]

Values are mean (n = 7) ± SEM. Values with different alphabets in each column are significantly different at $^{*}p < 0.05$
One unit of NiOS is defined as the amount of the enzyme that oxidizes 1 mole of $NADPH^{=}$ per hour at 37 °C.

Table 4: **The effect of administration of monosodium glutamate (MSG) and ivermectin (IVER) on the activities of acid phosphatase (ACP) and alkaline phosphatase (ALP) in rat brain**

Groups	ACP µmol mg^{-1} protein min^{-1}	ALP µmol mg^{-1} protein min^{-1}
Control	14.45±1.04[a]	89.30±6.51[a]
MSG	6.18±0.51[b]	22.73±2.11[b]
MSG+IVER	15.16±1.31[a]	91.17±7.21[a]
IVER after MSG	7.01±0.43[b]	23.11±2.01[b]

Values are mean (n = 7) ± SEM. Values with different alphabets in each column are significantly different at $^{*}p < 0.05$

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DISCUSSION

Sharma (30) demonstrated that administration of monosodium glutamate (MSG) at high concentrations induces oxidative stress in different organs. Oxidative stress is a characteristic feature in a number of neurodegenerative disorders such as stroke, Parkinson's disease and Alzheimer's disease (31). The brain is particularly vulnerable to oxidative stress injury because of its high rate of oxidative metabolic activity (32), high content of polyunsaturated fatty acids, relatively low antioxidant capacity, the abundance of redox-active transition metal ions (33) and nonreplicating nature of its neuronal cells (34). Oxidative stress results from an imbalance between the concentration of free radicals (reactive oxygen species) and the antioxidant system (35). In order for reactive oxygen species (ROS) to be scavenged, different defense systems known as antioxidant enzymes (such as superoxide dismutase, glutathione peroxidase, and catalase) and nonenzymatic (e.g glutathione) are present in the brain (32). Another possible action of MSG is through the activation of the glutamate receptor channels which induce the flux of Ca^{2+} into the cytosol from the stored vesicles and/or outside the cell. Elevated Ca^{2+} concentration can activate various Ca^{2+}-dependent degradative enzymes (e.g., phospholipases, proteases, endonucleases), which may contribute to cell death (36). This mechanism can also occur through oxidative stress. Oxidative stress may cause impairment in the transport and subsequent perturbation of intracellular calcium ion homeostasis, resulting in a sustained increase in cytosolic calcium ion level.

In addition to the brain antioxidants, the blood-brain barrier is an important neuroprotective device regulating the movement of substances into the brain (37). *p*-glycoprotein is an essential constituent of the blood-brain barrier (BBB). Many macrocyclic lactones interact differently with *p*-glycoprotein and have different *p*-glycoprotein efflux potential. The efflux activity of mamma-lian multidrug resistance protein 1 (mdr1) appears to be critically important for preventing central nervous system toxicity by ivermectin and other avermectins (38). Despite the wide range of biological effects, the cellular and molecular mechanisms of action for macrocyclic lactone ring-containing compounds on neuroprotective effects are yet to be known but it is likely that they are partly mediated by altered calcium ion transport across the endoplasmic reticulum, similar to those reported in the reticulum of the sarcoplasm (39). Another possibility is that the interaction of ivecmetrin with *p*-glycoproteins may impair the transport function of the BBB (40) thereby preventing the influx of toxins across the barrier.

The significant increase in GST activity and drop in GSH concentration of the rats administered MSG alone for 21 days and those that later received ivermectin orally is an indication that free radicals-induced oxidative stress is in part the mode of action of excitotoxic effects of MSG. Reduced glutathione is a substrate for conjugation reaction, an important step in the detoxification process with its thiol (SH) group being a reducing agent and offer protection from oxidative damage caused by reactive oxygen species (41). GSH can diminish oxidative stress either through protection of the detoxifying enzymes by increasing the efficacy of nicotinamide adenine dinucleotide phosphate (NADPH), or by helping in the elimination of compounds which produce peroxidation in the cell membranes (42). This perhaps may be among other reasons for the decreased level of GSH observed in this study. The decrease in GSH concentration recorded from this study is in accordance with the report of Neveen and Iman (32). However, the effect of co-administration of MSG and ivermectin on the rats is possibly due to the interaction of ivermectin with the BBB *p*-glycoproteins thus preventing the increased accumulation of MSG in the brain. Glutamate does not easily cross the blood-brain barrier; rather, it is transported as a result of high affinity transport system (43), as it has been proposed that ivermectin is a substrate of p-glycoprotein (44). Therefore, *p*-glycoprotein may have a greater affinity for ivermectin, which may continue to mediate the efflux of ivermectin, there-by negating the influx of MSG and consequential accretion in the brain.

This is supported by the non-significant change in all the parameters studied for this group of rats, indicating the absence of oxidative stress or excitotoxicity due to MSG.

Glutathione-S-transferase (GST) catalyzes the transfer of tripeptide glutathione to endogenous and xenobiotic substrates that has electrophilic functional groups (45). An increase in the concentration of any of the enzyme's substrate increases its activities (46). Thus, the increase in GST activity in the group administered MSG alone and that administered ivermectin after 14 days administration of MSG may be attributed to the substrate effect of MSG or ivermectin on the high affinity transport system (43). Peroxidation of lipid yields malondialdehyde (MDA) as a major aldehyde product. It is an autocatalytic mechanism that leads to the oxidative damage of cellular membranes (47). The brain is exceptionally predisposed to oxidative damage because polyunsaturated fatty acids are one of its essential

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membrane components (48), which culminate in escalated peroxidation. An increase in MDA in groups 2 and 4 is an indication of increased peroxidation of lipids in the brain, consequent of the increased level of reactive oxygen species. This change was not observed in group 3 rats possibly due to the prevention of MSG influx as a result of the ivermectin-*p*-glycoprotein interaction.

The effects of oral administration of MSG and ivermectin on calcium transport was evaluated by assaying for intracellular Ca^{2+} level, and Na^+ - K^+ and Ca^{2+} - Mg^{2+} ATPase activities. The significant increase in Ca^{2+} level observed in both MSG-treated and ivermectin after MSG-treated groups can be attributed to two reasons; glutamate induction of calcium release from the endoplasmic reticulum inside the cell and oxidative stress-induced impairment of Ca^{2+} transport and subsequent perturbation of intracellular Ca^{2+} homeostasis, resulting in a sustained increase in cytosolic Ca^{2+} concentration. The latter is supported by the significant decrease in Na^+ - K^+ and Ca^{2+} - Mg^{2+} ATPase, reducing the active efflux of Ca^{2+} from the cell. This corroborates the report that MSG caused damage to mitochondria from excessively high intracellular Ca^{2+} (30). Nitric oxide synthase (NiOS) catalyses the formation of nitric oxide (NO) from arginine. NO is believed to be an important cellular signaling molecule that acts as a retrograde neurotransmitter. It is produced by NiOS as a defence mechanism.

The induction of high-output of NiOS usually occurs in an oxidative environment, and thus high levels of NO have the opportunity to react with superoxide radical to form peroxynitrite and subsequently cause cell toxicity (49). The non-significant change observed in the NiOS activity of rats in group 3 indicated the non-oxidative state of the brain tissue. This is further justified by a non-significant change in SOD and catalase activity of the rats. The prevention of influx of MSG possibly by ivermectin-*p*-glycoprotein interaction may also be attributed to this observation. The increased activities of SOD and CAT enzymes in rats administered MSG and those that received ivermectin for 7 days after MSG in the present study is in accord with the reports of Farombi and Onyema (50).

The significant reduction in the brain ACP and ALP of the MSG and ivermectin after MSG-treated groups is suggestive of the possible lysosomal membrane and plasma membrane damage, respectively. This may be a consequence of leakage in the membranes resulting in loss of theses enzymes into the surrounding fluids. The significant escalation in MDA concentration observed in this present study is an indication of an alteration of membrane integrity. Administration of MSG to neonatal rats during the first week of life has been documented to induce a neurodegenerative process, which is presented by several neurochemical alterations of surviving neurons in the brain (51). In addition, Bojanić et al. (8) hypothesized that the alteration in the permeability of the neural membrane and subsequent degradation may be caused by a high concentration of MSG. The effect of co-administration of MSG and ivermectin on ACP and ALP activities is in line with the earlier observation that ivermectin in the presence of MSG may have caused a reduced influx of MSG into the brain cells possibly through the *p*-glycoprotein of BBB.

CONCLUSION

The present study suggests that ivermectin may exert an important role in protecting against neuro- and excitotoxin when co-administered. This may occur possibly through the interaction of ivermectin with the *p*-glycoprotein of the blood-brain barrier, thus causing a reduced influx of MSG into the brain. However, this study gives ways for further investigation on the effect of ivermectin on brain cell glutamate channels and Ca^{2+} pump under conditions of excitotoxicity induced by MSG.

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Original article

Ivermektin deluje zaštitno kod ekscitotoksičnosti izazvane natrijum glutamatom kod miševa

Rotimi O. Arise[1], Abimbola K. Arise[2], Oluwole I. Oyewole[3], Sylvia O. Malomo[1]

[1]*Departman za biohemiju, Univerzitet u Ilorinu, Ilorin, Nigerija*
[2]*Departman za domaćinstvo i nauku o hrani, Univerzitet u Ilorinu, Ilorin, Nigerija*
[3]*Odsek za biohemiju, Departman za hemijske nauke, Državni univerzitet Osogbo, Nigerija*

SAŽETAK

Utvrđeno je da natrijum glutamat (MSG), kao ekscitotoksični aditiv u ishrani, izaziva oksidativni stres u svim tkivima. Da bi se ispitali zaštitni efekti ivermektina na ekscitotoksičnost izazvanu MSG-om, dvadeset osam albino miševa muškog pola je podeljeno u četiri grupe. Prva, kontrolna grupa, je oralno primila 1ml destilovane vode; druga grupa je primila vodeni rastvor MSG-a (4 mg/kg telesne mase/ dnevno). Treća grupa je istovremeno primila istu dozu MSG-a i 0.4 mg/ kg telesne mase/ dnevno ivermektina, dok je četvrta grupa miševa oralno primala istu dozu MSG-a u toku dve nedelje, nakon čega je iveremektin oralno administriran nedelju dana. Davanje MSG-a oralnim putem u trajanju od 21 i 14 dana, nakon čega je usledilo oralno davanje ivermektina u trajanju od sedam dana, značajno je povećalo ($p < 0,05$) aktivnost glutation-S-transferaze, azot-oksid sintaze, superoksid dismutase, kao i koncentracije malondialdehida i intracelularnog Ca^{2+}, dok je aktivnost Na+ - K+ - ATPase, Ca^{2+} - Mg^{2+} - ATPase, kisele fosfataze i bazne fosfataze značajno opala ($p < 0,05$) u poređenju sa kontrolnom grupom. Međutim, istovremeno davanje MSG-a i ivermektina u trajanju od 21 dana nije pokazalo značajnu razliku ($p > 0,05$) kod svih parametara u poređenju sa kontrolnom grupom. Rezultat ukazuje da ivermektin može da deluje zaštitno kod ekscitotoksičnosti izazvane MSG-om kod miševa.

Ključne reči: **natrijum glutamat, ivermektin, ekscitotoksičnost, oksidativni stres, glutamatski kanali**

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