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Original Research Article

The Effect of Monosodium Glutamate Ingestion on Spatial Memory and Cognitive Behaviour in Wistar Rats

Austin A. Ajah[1*], Victor Opuada Hart[1]

[1]Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, University of Port Harcourt, P.M.B. 5323, Choba, Port Harcourt, Nigeria

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***Corresponding author:** Austin A. Ajah
Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, University of Port Harcourt, P.M.B. 5323, Choba, Port Harcourt, Nigeria

Abstract

Monosodium glutamate (MSG), one of the most widely used food-additives in commercial foods gives a special aroma (umami) to processed foods. It's vital to brain metabolism and function. Adverse effects of MSG have been widely reported. However, there is scarcity of literature on the action of MSG on spatial memory and cognition. Hence, there is need to assess the effect of MSG ingestion on spatial memory and cognitive behavior in *Wistar* rats. 25 *Wistar* rats were randomly selected into five groups and treated for three weeks thus: Group 1 (control), Group 2 (0.7 mL MSG), Group 3 (1 mL MSG), Group 4 (1.5 mL MSG) Group 5 (0.1 mL Epinephrine). Neurobehavioral (Barnes, navigation, and handgrip) activities exhibited by the various groups were recorded and analyzed using ANOVA. In the Barnes maze test, there was a significant decrease ($p<0.05$) in escape time in group 4 when compared to the control for weeks 1 and 3. In week 1 of the Navigation maze test, group 4 animals spent less time ($p<0.05$) to navigate the maze when compared to the control. In week 1 and 3 of the handgrip test, animals in groups 2, 3 and 5 had a significant decline ($p<0.05$) in grip strength when compared to the control group; However, in week 2, only the animals in group 5 had a decline in grip strength ($p<0.05$) when compared to control. MSG did not cause any form of neurotoxicity, cognitive or motor decline in rats.

Keywords: Monosodium glutamate, brain, cognition, spatial memory.

1.0 INTRODUCTION

1.1 Background to the Study

Monosodium glutamate (MSG) is a sodium salt of L-glutamate and is one of the most widely used food- additives in commercial foods. Its application has increased over time, and it is found in many different ingredients and processed foods obtainable in every market or grocery store. Monosodium glutamate gives a special aroma to processed foods which is known as umami in Japanese (Xiong *et al.,* 2009). This taste sensation is also called "savoury" (Xiong *et al.,* 2009). Free glutamic acid produces Umami or pleasant savory taste, one of the five primary tastes (others are sweet, sour salty and bitter) (Kurihara, 2015). Glutamate occurs naturally in protein-containing foods such as cheese, milk, mushrooms, meat, fish, and many vegetables. Glutamate is also produced by the human body and is vital for metabolism and brain function (Food Insight, 2009).

The presence of MSG in food increases the palatability or alters and magnifies the desirable taste, thus it is an essential part of the human diet and commonly found in most Asian Western diets (Sreejesh and Sreekumaran, 2018). The body does not discriminate the glutamate from monosodium glutamate and natural foods. The glutamate released from food or from the MSG is absorbed into the enterocytes from the lumen (Sreejesh and Sreekumaran, 2018). Glutamate is an important oxidative substance for intestinal mucosa and additionally is a precursor for arginine, proline, and glutathione (Peng *et al.,* 2011). The function of glutamate includes learning and memory (Peng *et al.,* 2011). Glutamate interacts with four different receptors to send messages swiftly between and across nerve cells (Peng *et al.,* 2011). This fast signaling and information processing is an important aspect of learning and memory (Peng *et al.,* 2011). Glutamate is one of the most abundant excitatory neurotransmitters in the brain, acting through N-methyl-D-aspartate (NMDA) and α-

amino-3- hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors and plays a pivot role in learning and memory (Moneim *et al.,* 2018; Jinap and Hajeb, 2010). However, adverse effects of MSG have been widely reported.

The United States Food and Drug Administration (FDA) reported that an unknown percentage of the population might react to MSG and develop certain symptoms (Kazmi *et al.,* 2017). Such symptoms constitute a syndrome such as a burning sensation at the back of the neck, forearms and chest, headache, chest pain. Other symptoms include facial pressure/tightness, nausea, palpitation, numbness at the back of the neck, radiating to the arms and back, tingling, warmth, weakness in the face, temples, upper back, neck and arms, drowsiness, and weakness. These symptoms are collectively called MSG symptom complex (Kazmi *et al.,* 2017). There are no accessible data on the effect of MSG among Africans as well as Nigerians. However, literature showed that monosodium glutamate was associated with adverse effects particularly in animals. Such adverse effects include obesity, diabetes, hepatotoxic, neurotoxic, and genotoxic effects (Geha *et al.,* 2000). Different reports revealed increased hunger, food intake, and obesity in human subjects (Geha *et al.,* 2000).

Additionally, animal studies have shown that increased administration of MSG resulted in an increased blood glutamate level (Bogdanov *et al.,* 1996). Therefore, neonatal administration of MSG leads to series of abnormalities in the brain (Boonnate *et al.,* 2015). These include immature blood brain barrier (Boonnate *et al.,* 2015), degenerative changes in hypothalamic arcuate nucleus (Holzwarth-Mcbride *et al.,* 1976), reduced serotonin and cognitive functioning (Moneim *et al.,* 2018), pyknotic Purkinje and granule cells with inflamed cells in the cerebellum (Strackx *et al.,* 2012). Another study showed that MSG treated group had an increase in the body weight, but mild doses did not show any increase in the body weight (Nusaiba *et al.,* 2018). Therefore, the present study investigates the effect of monosodium glutamate ingestion on spatial memory and cognitive behaviour in *Wistar* rats.

Monosodium glutamate has been proved to be toxic for both humans and experimental animals (Said and Nawal, 2012). Side-effects reported by various studies can be summarized as appearance of anomalies of metabolic/digestive, respiratory, circulatory, and nervous systems (Geha *et al.*, 2000). It was found that exposure of rats to MSG at neonatal stage can severely damage their hypothalamic nuclei (arcuate nucleus and ventromedial nucleus), which results in increased body weight, fat deposition, decreased motor activity, and secretion of growth hormone (Nakagawa *et al.,* 2000). However, there is scarcity of literature on the action of MSG on spatial memory and cognition. Hence, there is need to assess the effect of monosodium glutamate ingestion on spatial memory and cognitive behaviour in *Wistar* rats.

2.0 MATERIAL AND METHODS

2.1 Drugs and Chemicals

The drug, monosodium glutamate was bought from a mall and was used in this study. The monosodium glutamate was diluted in 20 ml of distilled water and was stored in a plastic bottle. Epinephrine was purchased from Sigma Chemicals (St Louis, MO, USA).

2.2 Experimental Animals and housing

25 Wistar rats of comparable sizes of 160 – 180g were bought from the Animal House of the Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, University of Port Harcourt, Nigeria. The animals were housed in a forced air facility before and during the experiment at the Animal House in the University of Port Harcourt. The animals were maintained in the cages at 23°C and 50 – 60% relative humidity, with maximum ventilation. The groups were kept in separate compartments of different plastic cages measuring 23.5 x 16.5 x 12cm (length, height, and width respectively) and were always given water and feeds *ad libitum*. The experiment described in this report was conducted in accordance with the National Institute of Health (2002) guide for the care and use of laboratory animals. These guides were approved by the institutional ethics committee for animal experiment.

2.2.1 Acclimatization of Animals

The rats used for the study were acclimatized for two weeks at the animal house to observe them before the commencement of the experiment under standard laboratory condition in a well-ventilated standard housing condition.

2.3 Ethical Statements

The experimental procedures and techniques used in the study were in accordance with acceptable principles for laboratory animal use and care by NIH, 1985 and EU directive of 1989:86/609/EEC. All conditions and handling of the animals were approved by the Ethical Committee of Faculty Basic Medical Sciences, University of Port Harcourt, Nigeria.

2.4 Preparation of Treatment

The drug, monosodium glutamate was bought in a mall and was used in this study. The monosodium glutamate was diluted in 20 ml of distilled water and was stored in a plastic bottle.

2.5 Experimental Design and Animal Grouping

A total of 25 Wistar rats were randomly selected and divided into five groups of 5 rats per

group. They were treated for three weeks thus: Group 1 (control), Group 2 (0.7 mL MSG), Group 3 (1 mL MSG), Group 4 (1.5 mL MSG) Group 5 (0.1 mL Epinephrine). The experimental design is as summarized in table 1 below.

Table 1: The experimental design showing the group, treatment, test, procedure and duration

Groups	Treatment	Neuro-Behavioural test	Procedure and Duration
Group 1	Control (5 rats)	Navigation test, Barnes maze test, and handgrip test	The rats were exposed to the amnestic test without any drug treatment for 3 weeks
Group 2	0.7ml monosodium glutamate mixture	Navigation test, Barnes maze test, and handgrip test	The rats were exposed to the amnestic test with 0.7 ml of monosodium glutamate mixture for 3 weeks
Group 3	1ml monosodium glutamate mixture 5 rats	Navigation test, Barnes maze test, and handgrip test	The rats were exposed to the amnestic test with 1 ml of monosodium glutamate mixture for 3 weeks
Group 4	1.5ml monosodium glutamate mixture 5 rats	Navigation test, Barnes maze test, and handgrip test	The rats were exposed to the amnestic test with 1.5 ml of monosodium glutamate mixture for 3 weeks
Group 5	0.1ml Epinephrine 5 rats	Navigation test, Barnes maze test, and handgrip test	The rats were exposed through the amnestic test with 0.1 ml of epinephrine for 3 weeks

2.6 Neuro-Behavioural studies

2.6.1 Barnes Maze

The Barnes maze is a tool used in psychological laboratory experiments to measure spatial learning and memory. The test subjects are rodents such as mice or lab rats. It is a visual-spatial learning and memory task designed for rats. It consists of an elevated circular surface with holes around the edge. It is an instrument used in psychological laboratory experiments to measure spatial and learning memory (Barnes, 1979). The study of spatial memory led to Barnes maze development, originally for rats and later adopted for mice (Bach *et al.*, 1995; Barnes, 1979). Rodents utilize extra-maze visual cues to locate an escape hole and can escape from open space and bright light into a dark box beneath the maze. Time taken to locate the escape hole into the dark box beneath the maze is then recorded.

2.6.2 Navigational task

The two main parts of the cognitive navigation process are movement and way discovery. Locomotion is the term for an animal's real bodily movement when it is moving through its immediate environment. Making decisions involves using the process of locating a destination through orientation and landmark location, which is a component of way finding. The Navigation box was disinfected with 70% ethanol at the end of each experiment to pave way for the next experiment. Animals were placed in the box through the entrance door and immediately the stopwatch was start. Animals placed in the box were allowed to find their way through the environment without getting lost at a maximum time of 300 seconds (5mins). The procedure was repeated for all the animals and the test were performed for 3 consecutive days with 3trials carried out on each of the days. After each trial, the apparatus was cleaned to remove residual smell and faecal contents from previous rat.

2.6.3 Handgrip Test

The grip strength test is a simple non-invasive method designed to evaluate mouse muscle force in vivo, by taking advantage of the animals' tendency to grasp a horizontal metal bar or grid while suspended by its tail, this test is also used to measure grip-strength (i.e., peak force and time resistance) of forelimbs and hind limbs in rats. The modified method as described by (Takeshita *et al.,* (2017) was used for this work.

2.7 Method of Data Analysis

Statistical data were analysed using GraphPad Prism 8 software (Graph-pad Software Inc., San Diego, USA). Multiple-group parametric data were analysed by one-way analysis of variance (ANOVA), expressed as mean ± standard error of mean (SEM); followed by a Tukey's *post hoc* test for multiple group comparisons. Data was considered statistically significant when $p \leq 0.05$.

3.0 RESULTS

The results of the outcomes of this research are presented as graphs as represented in the next page.

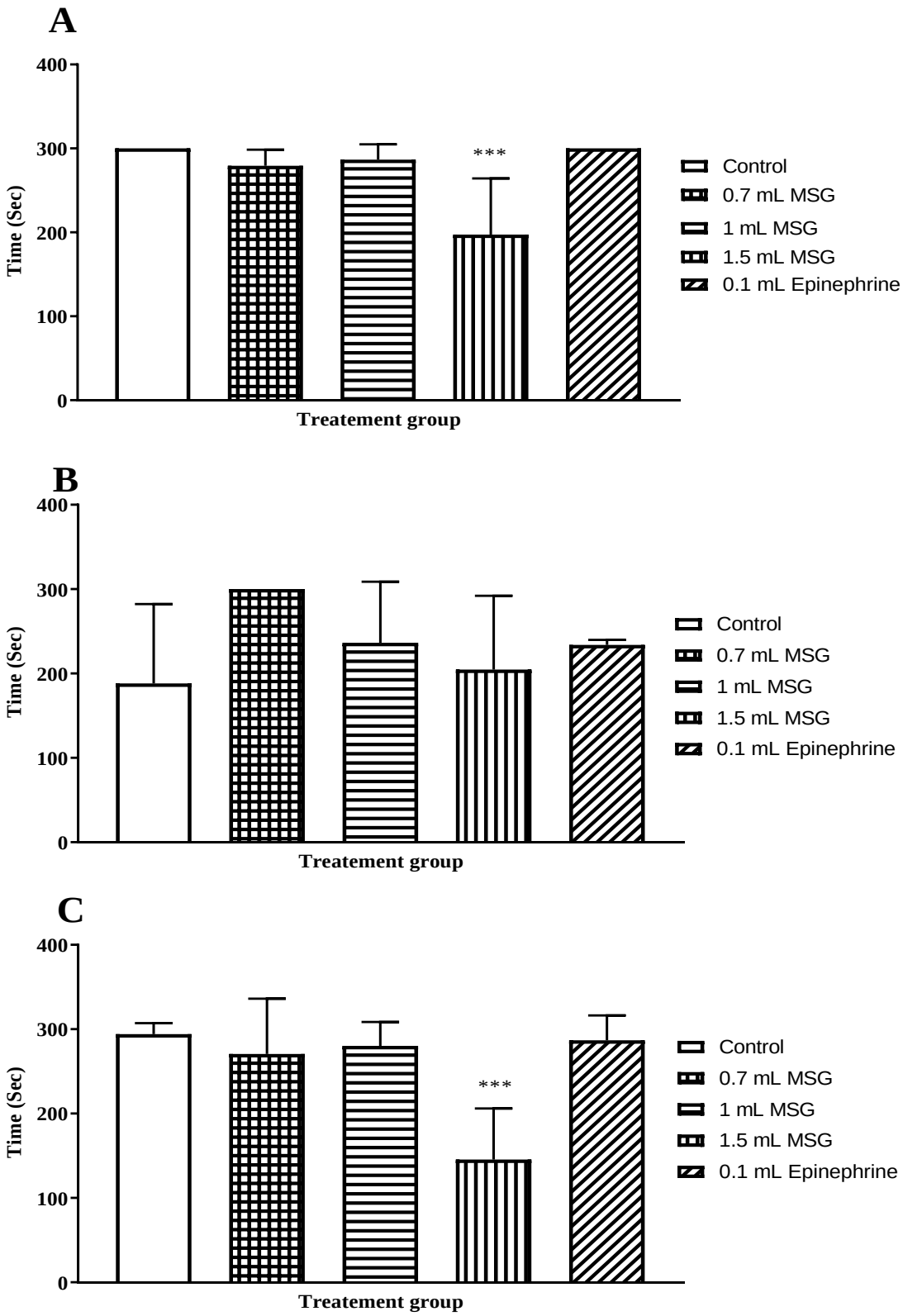

Figure 1: The effect of monosodium glutamate ingestion on spatial memory and cognitive behaviour in rats using Barnes maze test. A = Week 1, B = Week 2, and C = Week 3); Results are presented as mean ± SEM. N=5, * Mean values are statistically significant when compared to the control group

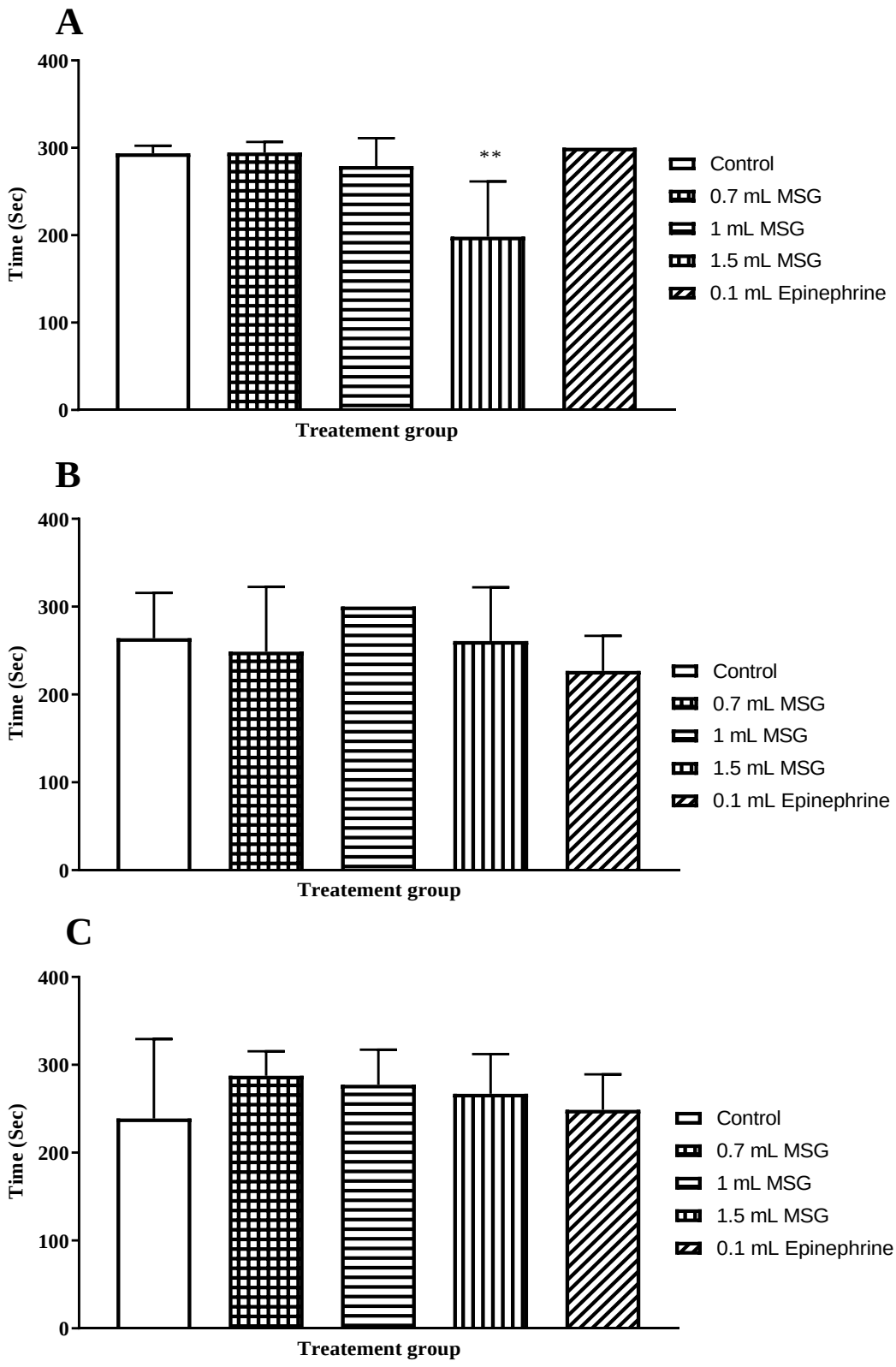

Figure 2: The effect of monosodium glutamate ingestion on cognitive behaviour in rats using navigation maze test. A = Week 1, B = Week 2, and C = Week 3); Results are presented as mean ± SEM. N=5, * Mean values are statistically significant when compared to the control group

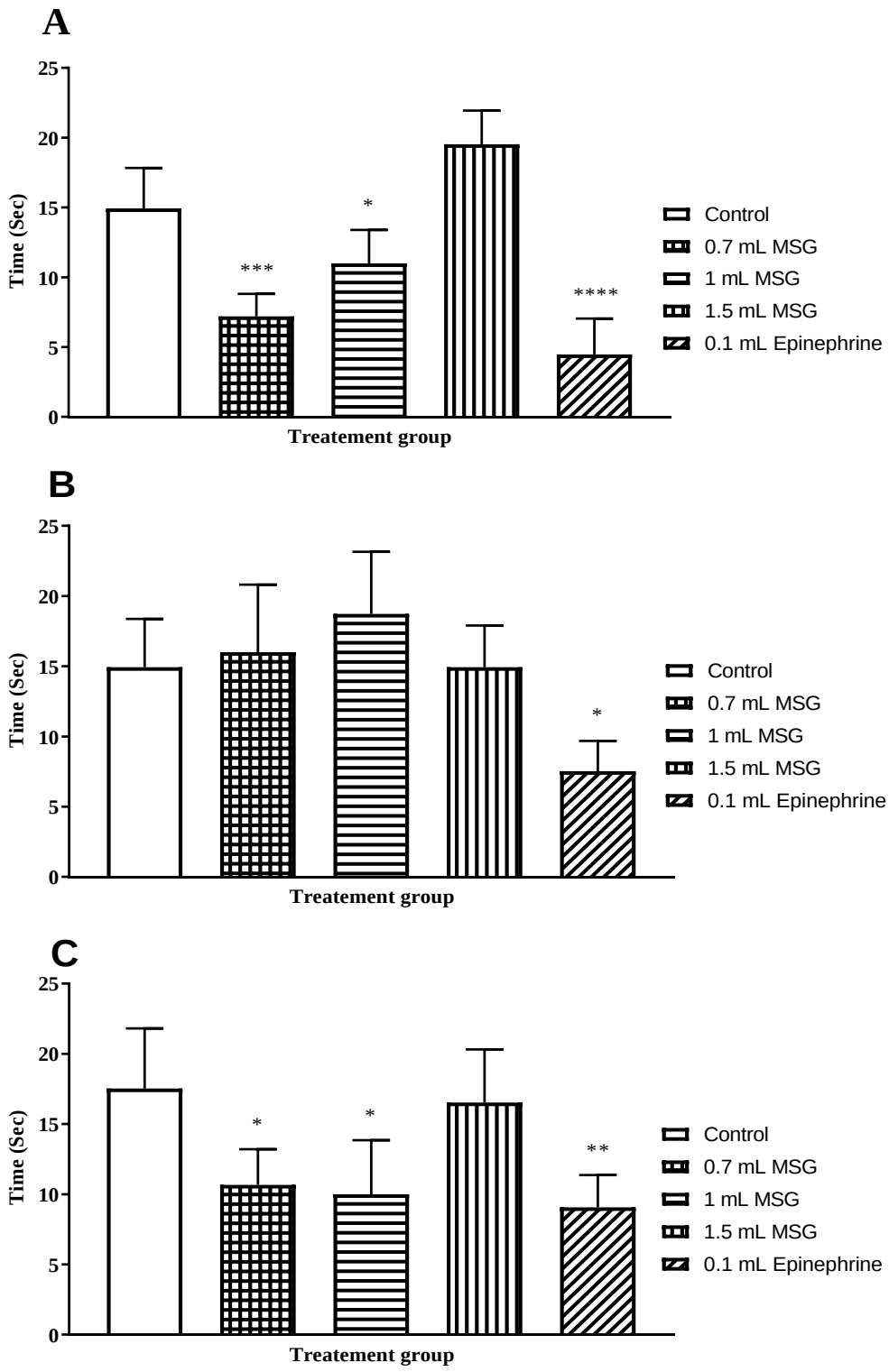

Figure 3: The effect of monosodium glutamate ingestion on spatial memory and cognitive behaviour in rats using handgrip test. A = Week 1, B = Week 2, and C = Week 3); Results are presented as mean ± SEM. N=5, * Mean values are statistically significant when compared to the control group

4.0 DISCUSSION

Monosodium Glutamate (MSG) is one of the world's most extensively used food additives which is ingested as part of commercially processed foods (Husarova and Ostatnikova, 2013). The glutamate industry often uses flavours in ingredients labeled "flavour," or "flavoring," (this preceded by the word

"natural"). They use "reaction flavors" as "clean label" alternatives to the use of "monosodium glutamate".

The present study evaluated the effect of monosodium glutamate ingestion on spatial memory and cognitive behavior in Wistar rats. Following ingestion of monosodium glutamate, analysis of the result from the spatial memory and cognitive behavior test as shown in graphs above are discussed as follows:

Barnes Maze

Figure 1 shows results for spatial memory and learning assessment in the test and control groups using Barnes maze. The Barnes maze is a test in which rats use extra-maze visual cues to locate an escape hole that allows them to escape from open space and bright light into a dark box beneath the maze. The time it takes to locate the escape hole into the dark box beneath the maze is recorded. From the result obtained from this study, animals administered 1.5ml of MSG escaped the Barnes maze at a quicker time when compared to the control weeks 1 and 3. The Barnes maze (spatial memory) is a dry land based behavioral test that has been shown to be sensitive to spatial learning related to neurodegeneration (Morgan and Curran, 2008). The result obtained from Barnes maze test in the current study showed that in week 1, the time spent in in the performance of the visual scene-based memory task was distorted across the test groups when compared to the group treated with epinephrine and similar result was obtained in week 2 and 3. A dose- and time-dependent pattern of effect was observed as presented in figures 1A and B. It has been suggested that MSG induces inhibitory effects on spatial learning and memory by destroying *Arc mRNA* (Penrod *et al.,* 2020). *Arc/Arg3.1* fosters the maturation of hippocampal network activity necessary for learning and memory storage (Penrod *et al.,* 2020). The destruction of Arc mRNA can affect the learning and memory function of hippocampus (Penrod *et al.,* 2020). This study is in contrast to the findings of (Moneim *et al.,* 2018), who reported a cognitive decline in 5-6 weeks old Wistar rats following 30 days oral administration of MSG. However, (Kouzuki *et al.,* 2019) reported an improvement in cognitive behaviour following ingestion of MSG in demented patients.

Navigation maze

Figure 2 shows result of motor and locomotion assessment in the test and control groups using navigation maze test after 3 weeks of ingestion of monosodium glutamate in Wistar rats across the groups. Animals were placed in the navigation maze box and allowed to find their way through the environment at a maximum time of 300 seconds (5mins). The procedure was repeated for all the animals and the test were performed for 3 consecutive days (day 1, 3 and 5 respectively) with 3trials carried out on each of the days. Navigation through an inter-connecting pathway within a given task time was taken as a measure of memory recall and cognito-motor performance. From the result presented in Figure 2, it was observed that the animals administered 1.5ml of MSG (Rats in group 4) spent less time in navigating the maze in week 1 when compared with control.

The decrease in time spent in executing the task by animals administered 1.5ml of MSG shows that ingestion of MSG did not cause neurotoxicity, which did not result to cognitive and locomotive impairment. The speed of task performance was a measure of learning from pre-exposure and spatial memory. Completion of task as fast as possible could be tantamount to mental proficiency and could leave a restorative and reversible pathway in the motor system (Biradee and Olorunfemi, 2020). The finding of the current research corroborates that of, (Kouzuki *et al.,* 2019) who reported an improvement in cognitive behaviour following ingestion of MSG by patients with dementia.

Handgrip

Assessment of Cognito-motor functions in the test and control groups using Handgrip Task are presented in figure 3. The handgrip task is used to evaluate motor function and deficit in experimental models by sensing the peak amount of force an animal applies in grasping specially designed pull bar assemblies. Result obtained in week 1 and 3 of this study showed that animals in groups 2, 3 and 5 had a significant decline in grip strength when compare with the control group. However, in week 2, only the animals in group 5 had a decline in grip strength when compared with control. This is to say that at a higher dose of MSG (1.5 mL), animals tend to have a better motor function than in lower doses. The grip strength is improved in a dose dependent manner.

From the result in figure 3, it can be seen that animals administered MSG showed better grip strength than the epinephrine administered groups (5) from week 1 to week 3. This shows that at higher allowable dose, MSG improves motor function as it resulted in higher grip strength. The result of the current study contrasts with that of (Prastiwi *et al.,* 2015) (Prastiwi *et al.,* 2015), who reported that higher dosages, but not lower dosages caused a significant decrease in motor coordination in adult male Wistar rats. This discrepancy could be because of the age of the rats used in the various studies, as our rats were older than that of the previous study (Ghasemi *et al.,* 2021).

All experimental tasks for assessing psychomotor function in this study showed that ingestion of higher doses of MSG improves spatial memory and cognitive function in experimental animals.

This is also noted in the result obtained in the week 1 and 3 of the Barnes maze and navigation maze tests, where the animals in group 4 located the escape cues faster than the animals in the rest of the groups when compared with the control groups. That is to say that the animals in group 4 in the Barnes maze, Navigation maze and handgrip tests were intact and MSG at a higher dose improves learning and memory.

Kiss *et al.,* (2005) observed that MSG treatment in neonatal rats does not cause permanent alterations in the neurobehavioral development later in adulthood. Also, Kouzuki *et al.,* (2019) suggested that continued ingestion of MSG has a positive effect on cognitive function. This was further validated and concluded that MSG showed improvement in cognitive function when administered to patients with dementia. The current study corroborates the findings of the previous studies.

Therefore, in conclusion, following the finding of this current study and that of previous studies, it can be suggested that ingestion of MSG within the allowable limits is safe and does not cause any form of neurotoxicity, cognitive or motor decline in rats. In the future, we recommend that mechanistic study be carried out to examine the mechanism in which MSG carries out its memory and motor coordination activities.

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