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Evaluation of the Effect of Caffeine on the Cerebellar Cortex of Mercury Treated Wistar Rats

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ABSTRACT

Mercury is a toxic heavy metal that constitutes a significant environmental and health problem, with evidences indicating the central nervous system as the main target. This study was therefore designed to evaluate the effect of caffeine on the histology of the cerebellum of mercury treated Wistar rats. Twenty adult male Wistar rats were distributed into four groups (n=4). Administration was as follows: Control (distilled water, 1 ml/kg), mercury chloride ($HgCl_2$), 16.6 mg/kg body weight, low dose caffeine (20.7 mg/kg) with mercury chloride (16.6 mg/kg), high dose caffeine (41.5 mg/kg) with mercury chloride (16.6 mg/kg). The administrations lasted for 28 days via oral route daily. Histological evaluation was carried out with haematoxylin and eosin, and cresyl violet stains. Beam walking test (BWT) for motor coordination was carried out. Alteration in the cerebellar cortex histoarchitecture seen in mercury chloride group was ameliorated in the groups treated with caffeine. The result of BWT test showed an increase in the time taken to locate the platform after mercury chloride administration but was decreased after administration of caffeine ($p>0.05$). The administration of caffeine protect against mercury chloride toxicity to the cerebellum of Wistar rats.

Key words: *Mercury chloride, Caffeine, Wistar rats, Cerebellum*

INTRODUCTION

Interaction of man with his environment exposes him to a range of heavy metals (Burger et al. 2011) that affect major systems in the body (McDowell 2003). This interaction which is due to advancement in technology and improvement in standard of living brought unrestrained industrialization and urbanization without proper emission and pollution controls (Bennett et al. 2003). This posed a major challenge to environmental safety as the heavy metals are widely utilized to sustain the standards of living in the modern world (Arif et al. 2015). Mercury chloride ($HgCl_2$) is commonly found in antiseptics, antifungal and anti-parasite materials. It is also an ingredient in skin lightening soaps, creams, eye makeup cleansing products and mascara (WHO 1991). Reported cases of mercury toxicity have been widespread in Sweden, Mexico, USA and the Minamata Bay (Takizawa and Osame 2001). In Nigeria, the use of Kohl (a traditional cosmetic) among some northern states such as Katsina, Sokoto, and Gombe also predisposes to mercury toxicity (Onyeike et al. 2002). Mercury exerts its toxicity by inducing oxidative stress and apoptosis in affected organs of which the brain is very sensitive. This is due to its ability to affect the antioxidant system in the cell, resulting in loss of membrane integrity and finally cellular necrosis (Diamond and Zalups 1998). It inhibits: production of brain tubulin cells (Pendergrass and Haley 1997a; Hock et al. 1998), production of neurotransmitters,

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calcium-dependent neurotransmitter release (Discalzi et al. 2000), dihydroteridine reductase (Hock et al. 1998), nitric oxide synthase (Pendergrass and Haley 1997b), blocks neurotransmitter amino acids (Moreno-Fuenmayor et al. 1996) and causes abnormal migration of neurons in the cerebral cortex (Belletti et al. 2002). Caffeine, a widely consumed central nervous system stimulant, is present in beverages, energy drinks and over the counter medication and has been reported to possess antioxidant properties and play a protective role on cellular damage (Kamat et al. 2000; Nikolic et al. 2003; Krisko et al. 2005) probably due to its primary metabolites, 1-methylxanthine and 1-methyluric acid. This study therefore investigated this protective role of caffeine against mercury toxicity in the cerebellar cortex.

MATERIALS AND METHODS

Materials/Chemicals used

Analytical grade of caffeine powder manufactured by Sigma Aldrich Chemical (St. Louis, MO, United States) was obtained from Rovet Scientific Nigeria, Limited. Analytical grade mercuric chloride of 99.5% purity manufactured by Loba Chemis (Colaba, Mumbai India) was obtained. Bouin's fluid, ketamine, graded alcohol, distilled water, molten paraffin wax, haematoxylin and eosin, cresyl fast violet stain and methylated spirit.

Ethical Clearance

Ethical clearance was obtained from the Ethical Committee on Animal Use and Care of Ahmadu Bello University, Zaria with approval number ABUCAUC/2018/043.

Experimental Animals

Twenty apparently healthy adult male Wistar rats, 3-4 months old and weighing 130-160 g were used for this study. They were obtained from the Animal House of the Department of Human Anatomy, Faculty of Basic Medical Sciences, Ahmadu Bello University, Zaria. The animals were housed in standard laboratory cages with soft wood shavings and free access to rat pellet chow and water *ad libitum*. Neurobehavioural assessment was carried out weekly throughout the duration of the study.

Experimental Design

Control received 1 ml/kg body weight of distilled water daily for 28 days. Following the known lethal dose (LD_{50}) of mercury chloride to be 166 mg/kg body weight (ATSDR 2011; Sadeeq et al. 2013), 10% (16.6 mg/kg) of the LD_{50} of mercury chloride was used in this study.

Mercury treated group received 16.6 mg/kg body weight of mercury chloride. Low dose caffeine and mercury group received 20.7 mg/kg of caffeine and 16.6 mg/kg body weight of mercury chloride. High dose caffeine and mercury group received 41.5 mg/kg of caffeine and 16.6 mg/kg body weight of mercury chloride. The administrations were orally, once daily for 28 days using a metal oropharyngeal cannula and a 1 mL calibrated hypodermic syringe.

Beam Walking Test

The method of Goldstein and Davis (1990) was used to assess motor coordination function in the rats.

The beam was 100 cm long and 2 cm wide, suspended horizontally from its ends at an elevation of 30 cm. One end was mounted on a narrow support connected to a start platform 10 × 10 cm, and the other end attached to a goal box (20 × 20 × 20 cm) (Rodrigues-Alves et al. 2009).

Prior to the test, the rats were habituated to the beam walking apparatus daily for 3 days, and were required to walk across the length of the beam from the start point to the goal box which served as the finish point. A bright light source was placed over the start point which motivated the rats to traverse the beam. A sawdust-filled box at the base served as protection for the falling rats. Beam-walk scores were based on an average of three trials. A trial began by gently placing the Wistar rat on the start point of the beam and allowed for 60 sec. If the rat located the goal box at the end or before the 60 sec, it was removed from the box. If the animal did not locate the goal box after 60 sec or did not move at all, it was gently guided along the length of the beam to the goal box and allowed to orient to the goal box for an additional 20 sec. The beam was cleaned with cotton wool and methylated spirit after each trial.

The latency (time until the animal's nose entered the goal box (up to 60 sec) was recorded as described by Abou-Donia et al. (2008). Rats that fell off the beam or did not enter the goal box were assigned latencies of 60 sec. The animals were also observed for foot slips on the beam.

Histological Method

Twenty four hours after the last administration, the animals were intraperitoneally administered ketamine hydrochloride (75 mg/kg body weight) and sacrificed. Brains were harvested, washed in normal saline and fixed in Bouin's fluid. They were processed for paraffin was embedded. Paraffin sections of cerebellar cortex were cut longitudinally prepared and stained in haematoxylin and eosin stain. Cresyl fast violet stain was used for demonstration of Nissl substance

Statistical Analysis

All the results were analysed using IBM Statistical package for social Sciences (SPSS version 23) and the results were expressed as mean ± SEM. The statistical significance between the means was analysed using repeated measures of ANOVA

because the experiment was repeated weekly over a period of 4 weeks and p-value ≤ 0.05 was considered significant.

RESULTS

Beam Walking Test

As the weeks progressed from 1-4, administration of mercury chloride and caffeine had no significant effect ($p > 0.05$) on the beam score when compared to the control. However, an increase was observed in beam latency time of the Wistar rats. Wistar rats in control group showed a decrease in beam latency time when compared to the experimental groups. This decrease was not significant ($p > 0.05$).

Histology

The cerebral sections of Wistar rats in the control group showed normal histoarchitecture of the cerebral cortex; the characteristic appearance of the three cortical layers; an outer molecular, the Purkinje cell and an inner granular. The cerebellar sections of Wistar rats treated with mercury showed an alteration of the cerebellar layers especially the Purkinje cell layer, necrosis of the Purkinje cells, and loss of Nissl substance from Purkinje cells. In the low dose caffeine group, there was presence of normal and few vacuolated Purkinje cells. Cerebellar sections from animals in the high dose caffeine group showed mild neurodegeneration of the cerebellar layers with necrosis and cytoplasmic vacuolation of the Purkinje cells.

DISCUSSION

The present study investigated the effects of caffeine on motor co-ordination and the histoarchitecture of cerebellar cortex following administration of mercury.

Caffeine is a non-selective adenosine receptor antagonist, specifically for A_1 and A_2A receptors, with a low affinity for A_3 receptors (Karcz-Kubicha et al. 2003; Ferré 2008). These receptors are believed to be responsible for the behavioural effects of caffeine, and both receptor subtypes are expressed in the brain with higher levels of A_1 receptors found in the hippocampus, cortex, cerebellum and hypothalamus (Landolt 2008)

The beam walking test allows for a detailed evaluation of subtle motor impairments due to the challenge imposed on the animals in crossing narrow beams (Carter et al. 1999; Karl et al. 2003). Increase in mercury concentration in the cerebellum of Wistar rats was associated with disability in tasks requiring greater motor refinement as seen by poor performance (increase in latency time) of mercury treated Wistar rats on the beams although, this was not significant. Inorganic mercury is carried across the blood brain barrier by the L-type neutral amino acid transporter and accumulates in the brain of Wistar rats with highest accumulation in the cerebral cortex (Teixeira et al. 2014). Therefore, it may be suggested that the concentration of mercury that got to the cerebrum was more than what was present in the cerebellum of the Wistar rats and may account for the non-significant increase observed in the mean latency time of Wistar rats on the beam. Results obtained here was dissimilar to the work of Teixeira et al. 2014 who reported accumulation of inorganic mercury in the brain of Wistar rats at a dose of 0.375 mg/kg/day for 45 days with an alteration in motor coordination function. Administration of caffeine in the present study did not cause any significant decrease in mean latency of Wistar rats on the beam. However, previous researches have showed that high dose of caffeine could affect skeletal muscle contraction either through the stimulation of Ca^{2+} release from the sarcoplasmic reticulum (Mohr et al. 1998; Tarnopolsky and Cupido 2000) or by reducing the K^+ efflux (Mohr et al. 2011) which would affect motor function. In addition, it was found that a

Table 1: Mean beam latency for Wistar rats in beam walking test showing initial time and time after exposure to caffeine and mercury

	Initial	Week 1	Week 2	Week 3	Week 4	*F*	*p*
Control	5.71±1.81	7.72±3.82	3.55±1.56	2.77±0.38	2.27±0.45	1.323	0.335
16.6 mg/kg $HgCl_2$	3.74±0.52	3.57±0.84	4.75±1.66	9.96±3.72	26.34±10.5	3.739	0.108
20.7 mg/kg caffeine + 16.6 mg/kg $HgCl_2$	3.04±0.53	2.43±0.89	4.32±1.28	8.20±4.83	4.96±1.51	1.105	0.388
41.5 mg/kg caffeine + 16.6 mg/kg $HgCl_2$	6.64±2.13	4.13±0.64	3.64±0.69	7.78±2.05	11.97±3.45	1.877	0.216

Values obtained from the initial training time, and across the week was analyzed using repeated measure of ANOVA to compare the mean differences across the groups. A P>0.05 was obtained for the treatment groups and control. Therefore result obtained was not statistically significant and no post hoc test was carried out.

derivative of caffeine, theobromine up regulates cerebral brain-derived neurotrophic factor (BDNF) and facilitates motor learning in mice (Yoneda et al. 2017). Results obtained in this study is dissimilar to the study of Almosawi et al. (2018) who reported enhanced motor and spatial memory functions in mice treated with 20 mg/kg body weight of caffeine for one week.

Neurotoxicity in the nervous system is indicated by neurodegeneration and distortion of neural tissue (Nahla et al. 2011; Kalantaripour et al. 2012) and can corroborate toxicity which is indicated by oxidative damage (Jadhav et al. 2007). Histological examinations of the cerebellar cortex in the control and caffeine treated groups showed relatively little histological changes, while the cerebellar cortex of animals in the mercury only group showed evidence of neurodegeneration such as necrosis, cytoplasmic vacuolation and chromatolysis which could be as a result of oxidation within the cells. Degenerating neurons stain very poorly with cresyl fast violet due to disassociation of ribosomes from the rough endoplasmic reticulum (RER) which occurs in the early stages of cell degeneration (Garman 2011). Dissociation of ribosomes leads to depletion in protein synthesis which invariably affects the function of the Purkinje cells. This disorientation of the Purkinje cells affects the motor activity and other motor functions of the cerebellar cortex such as loss of fine movement, loss of grasping power, disturbance in maintenance of equilibrium and loss of regulation of muscle tone (Martin et al. 1998). This agrees to studies where heavy metals such as mercury, lead, cadmium and arsenic have been reported to have the capacity to induce oxidative stress by depleting antioxidant enzymes resulting to nervous tissues damage (Amal and Mona 2009; Fakunle et al. 2013; Farina et al. 2013 and Teixeira et al. 2018). This study is also in agreement with the work of Teixeira et al. (2018) who reported necrosis of cerebellar cells after exposure to 0.37 mg/kg mercury chloride. The Purkinje cells are the most sensitive cells of the cerebellar cortex to toxic substances, and they react to these noxious substances by undergoing degeneration, thus disappearing from their relative positions in the Purkinje cell layer (Jomova and Volko 2011; Farina et al. 2013).

The low dose (20.7 mg/kg) caffeine group showed better histological features when compared with the high dose (41.5 mg/kg) group and mercury treated group. This is attributed to the protective effect of caffeine due to its antioxidant ability observed at lower doses (Nobre et al. 2010; Cakir et al. 2017). Caffeine is able to reduce oxidative stress by interacting with hydroxyl radical which leads to oxidative de-methylation and generation of partially N-methylated xanthines such as theobromine, paraxanthine and theophylline (Stadler et al. 1996; Chung and Chay 1997). Caffeine may also have acted due to its ability to scavenge heavy metal from the brain cells, thereby reducing the concentration of mercury that was present to cause any damage. Caffeine essentially acts in the brain as the competitive antagonist of adenosine receptors. The high rate expression of adenosine receptors especially in the hippocampus and cerebellar cortex indicates that the neuroprotective effect of caffeine in these areas may be through adenosine receptors (Him et al. 2018). This ability of caffeine to reduce oxidat-

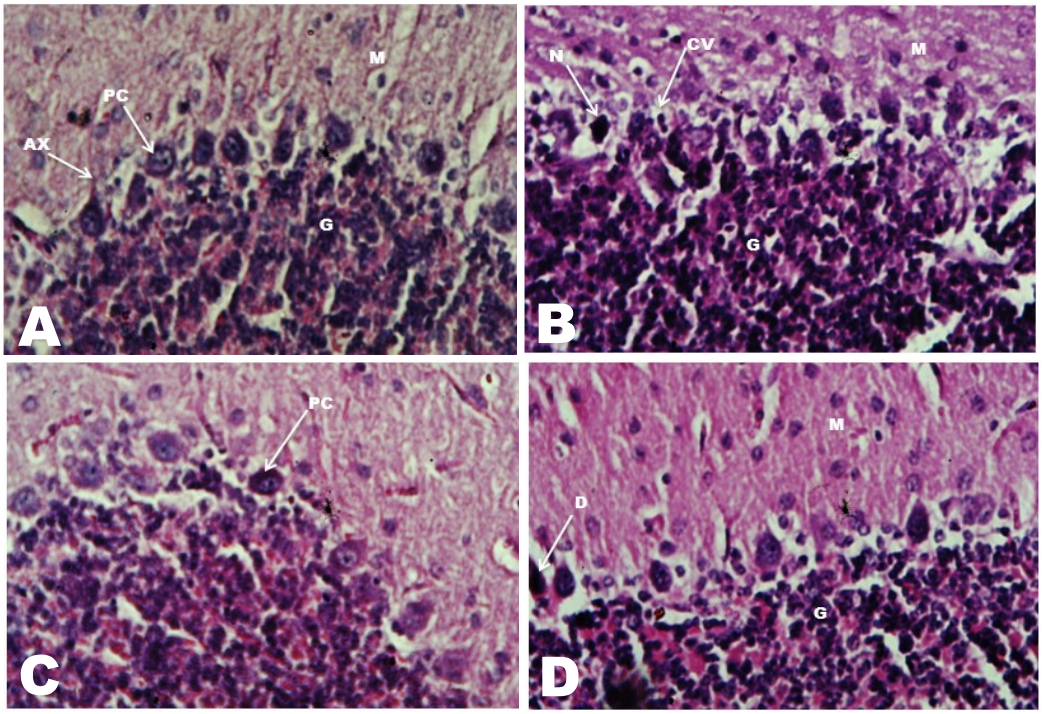

Figure I: Photomicrographs of sections of cerebellar cortex of Wistar rats stained with haematoxylin and Eosin. A: Control group with normal histoarchitecture of Molecular layer (M), Axon (AX), Purkinje cell (PC) and Granular layer (G). B: 6.6mg/kg mercury treated group with necrosis (N) and cytoplasmic vacuolation (CV) of the Purkinje cells. C: 20.7mg/kg of caffeine+ 16.6mg/kg Mercury treated group with normal Purkinje cells (PC) D: 41.5mg/kg caffeine+16.6mg/kg Mercury treated group with neurodegeneration (D) of Purkinje cells (H & E, Mag x250).

ive damage to the cells in this study suggests a protective role for caffeine against mercury toxicity. The result of present study was similar to the work of Him et al. (2018) who reported an improvement in neuronal number and neuronal degeneration after administration of caffeine to Wistar rats.

In the present study, increased mercury concentration in the cerebellum was associated with disability in task requiring greater motor refinement as seen by poor performance of mercury treated Wistar rats on the beams. At the end of the 4 weeks, an increase was observed in latency of the mercury treated groups to walk the beam to the escape platform when compared to the control group. Inorganic mercury has been shown to accumulate in the brain of Wistar rats thereby altering motor coordination function (Teixeira et al. 2014). Administration of caffeine to the animals showed a reduction in the latency to cross the beam when compared to animals treated with mercury only. This decrease in mean time may be due to the ability of caffeine to act as an antioxidant to relieve oxidative stress caused by mercury toxicity. Although other brain areas (motor cortex, basal ganglia) play an important role in fine motor control and fractionation of movement, the cerebellum plays a major role.

Neurodegeneration and histoarchitectural distortion of neural tissue are changes that are indicative of neurotoxicity in the central nervous system (Nahla et al. 2011; Kalantaripour et al. 2012) and can corroborate toxicity which is indicated by oxidative damage (Jadhav et al. 2007). Histological examinations of the cerebellar cortex in the control group, and caffeine treated groups showed the cytoarchitecture of the cerebellum with relatively little histological changes while the cerebellar cortex of animals in the mercury treated group only showed evidence of neurodegeneration which could be as result of oxidation within the cells. These changes include distortion of the cerebellar layer especially the Purkinje cell layer, loss of cellular architecture, loss of Nissl substance from Purkinje cells, and cytoplasmic vacuolation. Histological changes observed in the mercury treated group are supported by previous findings which showed that the Purkinje cells are the most sensitive cells of the cerebellar cortex to toxic substances, and they react to these noxious substances by undergoing degeneration, thus disappearing from their relative positions in the Purkinje cell layer (Jomova and Volko 2011; Farina et al. 2013). This was also in agreement to studies which showed that exposure to mercury chloride induces oxidative stress by depleting antioxidant system resulting in cell degeneration, loss of membrane integrity and necrosis (Ferraro et al. 2009; Teixeira et al. 2018).

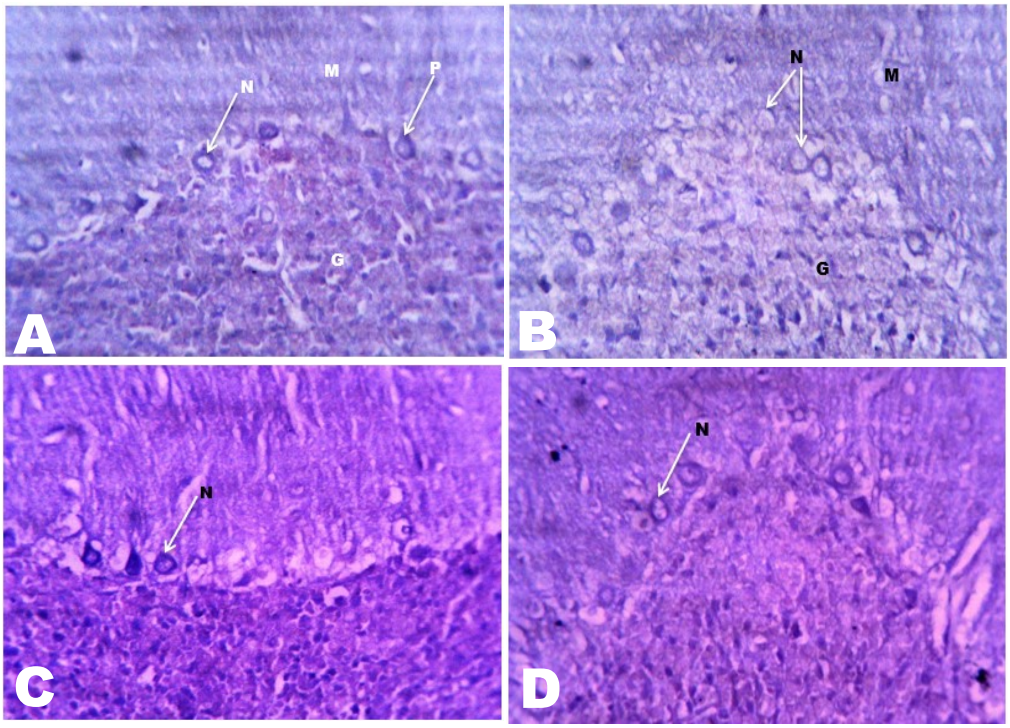

Figure 2: Photomicrographs of sections of cerebellar cortex of Wistar rats stained with cresyl fast violet. A: Control group revealed intense staining for Nissl substance (N), Purkinje cells (P). B: 16.6mg/kg Mercury treated group with reduced intensity for Nissl substance. C: 20.7mg/kg of caffeine+ 16.6mg/kg Mercury treated group with an increased intensity of Nissl substance. D: 41.5mg/kg caffeine+16.6mg/kg Mercury treated group with reduced staining intensity of Nissl substance (Cresyl fast violet, Mag x250).

Conclusion

The findings of the present study suggegest that caffeine can protect against mercury induced changes in the cerebellar cortex of Wistar rats.

Conflict of Interest

None declared.

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