Original Research Article

Cadmium chloride induced cognitive decline in female Wistar rats exposed to chronic restraint stress

ABSTRACT

Cadmium (Cd) is known to have someadverse effectson differentbiochemical and physiological functions causing neurotoxicity leading to neurodegeneration and increasing the risk factor for neurodegenerative disorders. Restraint stress is also associated with changes in behavioral, neuroendocrine function, and brain morphology. The study aimed to evaluate the effectsof cadmium chloride administration and restraint stress exposure on cognitive function of female Wistar rats. 24 female Wistar rats (180-220g) were randomly dividedinto 4 groups(n=6 each): Control (CTL), Restraint stress alone (RSS), Cadmium alone (CCC), Cadmium + Restraint stress (RSC).The experimental groups were subjected to cadmium chloride 100mg/kg orally andrestraint stress for 30 minutes.Prior to the animal sacrifice, behavioraltests were carried out to assess the effects of cadmium chloride and restraint stress on cognitive performance of rats. 24 hours post last cadmiumadministration and restraint stress exposure, all animals were anesthetized and sacrificed. The brainwas excised, weighed and homogenized for biochemical analysis (Serotonin and acetylcholinesterase activity). Resultsshowed that there was significant ($p<0.05$) decrease in serotonin level in Cadmium alone group when compared to the control group. The restraint stress + cadmium group showed a significant ($p<0.05$) increase in acetylcholine esterase level when compared control, cadmium alone and restraint stress alone groups. The findingsalso revealed that Cadmium exposure led to a significant ($p<0.05$) decrease on number of entries in open arms of elevated plus maze. Furthermore, spontaneous alteration (Y maze) was significantly ($p<0.05$) decrease in restraint stress alone, cadmium alone and restraint stress + cadmium groups when compared to the control group. In conclusion, cadmium exposure and restraint stress altered neurotransmission, increased anxiety-like

behavior, decreasedcognitive abilities, increasedalteration in hippocampal architecture and neuronal depletion as revealed in the histological evaluation resulting in cognitive deficits.

Keywords: Cadmium chloride, restraint stress, neurodegeneration,spontaneous alteration, cognitive deficit.

1.0 INTRODUCTION

Cadmium (Cd) is a highly toxic environmental pollutant absorbed into the human body via the respiratory system, gastrointestinal tract and skin (Das and Al-Naemi, 2019). Exposure to cadmium can be through food, water, cigarette smoke, and air contamination (Hayat *et al*., 2018). Its environmental half-life ranges between 25-30 years and accumulation of cadmium can resultsin a long termtoxicologicaleffect on multiple systems (Genchi*et al*., 2020).There are various sources of cadmium, it can be found naturally in the earth's crust, agriculture, and produced as a byproduct of mining (zinc, lead and copper) (Tomza-Marciniak et al., 2019; Haider *et al*., 2021). Bioavailability of this toxic heavy metal in the environment is due to increaseddomestic and industrial indiscriminate disposal into the water bodies and the soil (Mishra et al., 2019; Mallick et al., 2019). In this way cadmium gains access into the aquatic animals and crops, this is a secondary route of exposure. The nervous system is particularly vulnerable to cadmium toxicity, as prolonged exposure to cadmium disrupts the normal biochemical and physiological process in the nervous system (Tsentsevitsky and Petrov, 2021). The neurotoxic effect of Cd leads to alteration or disruption in various neurological functions such as memory and learning abilities (Elemile*et al*., 2023; Rezaei et al., 2024).Furthermore, cadmium exposure can impair the synthesis, release and reuptake of neurotransmitters such as serotonin and acetylcholine which playa key rolein cognitive process (Gonçalves*et al*., 2021).

Stress is any physical or psychological stimuli that disrupt homeostasis (Chu *et al*., 2024). Restraint stress is a commonly used experimental model for inducing stress response syndromes in animals (Atrooz*et al*., 2021; Sahin*et al*., 2019). Various studies have reported that restraint stress is associated with changes in behavioral, neuroendocrine function, and brain morphology, this makes it useful for researching the underlying mechanisms in stress-related neurological disorders.

Cognitive function is refers to range mental processes which includes memory, learning, attention, decision making and language abilities (Zhang, 2019). Serotonin and acetylcholine are neurotransmitters involved in the modulation of cognitive functions (Slater *et al*., 2022).Exposure to both acute and chronic stress is associated with cognitive impairment (Forghani *et al., 2024*).Serotonin and Acetylcholine are neurotransmitters that are involved in the modulation of cognitive function (Handra et al., 2019). Alteration in the levels of these neurotransmitters has a significant impact on cognitive function. Nevertheless, studies on thecombined effect of cadmium chloride and restraint stress on the cognitive functionin female Wistar rats are limited. Therefore, this study aimed to evaluate the effect of cadmium chlorideadministration and restraint stress on the cognitive function in female Wistar rats.

2.0 Material and methods

2.1 Chemical and compounds

Cadmium chloride (Kermel, China), chloroform, Normal Saline, distilled water, was purchased from department of pure and applied science laboratory, LAUTECH, Oyo State, Nigeria, Buffered formalin waspurchased from the department of Anatomy, FBMS, LAUTECH, Oyo State, phosphate buffer saline was purchased from department of science laboratory, LAUTECH, Oyo, Nigeria.

2.2 Experimental planning and Animals

Twenty-four (24) female rats (180-220g) were used for the study. The rats were kept in a standardized laboratory environment. The rats were acclimatized for two weeks and had free access to clean water and food. The rats were housed in standardized plastic cage maintained between 12-hour light and dark cycle. All protocols and treatment procedures were done according to guidelines of the Animal Research Ethical Committee of Ladoke Akintola University of Technology for the care and use of laboratory animals. All protocols and treatment procedures were done according to the Institutional Animal Care and Use Committee (IACUC) guidelines, in strict compliance with the National Institutes of Health (NIH) guideline for the care and use of laboratory animals. After acclimatization, the rats were divided randomly into four groups with six (6) rats in each group and the experiment lasted for 21 days. Group I represent the control group while groups II, III, IV servedas the experimental groups. The groups designate are: I=

Control group (CTL), II= Restraint Stress Alone (RSS), III= Cadmium Alone (CCC) and IV= Cadmium+ Restraint stress (RSC).

Table 1: Animal grouping and experimental procedures

GROUPS	**ADMINISTRATION**
Control (CTL)	Rats were given only animal feed and water *ad* libitum for 21 days.
Restraint Stress Alone (RSS)	Rats were subjected to restraint stress using wire gauze for 30 minutes daily for 21 days.
Cadmium Alone (CCC)	Rats received cadmium chloride (100mg/kg/b.w) orally for 21 days.
Cadmium+ Restraint stress (RSC)	Rats received cadmium chloride (100mg/kg/b.w) daily orally and were subjected to restraint stress using wire gauze for 30 minutes for 21 days.

2.3 Collection and Preparation of samples

On the last day of restraint stress induction or/cadmium chloride administration, behavioral assessments using Elevated plus Maze (Guedri*et al*., 2017) and Y maze (Yoshizak*et al*., 2020) were carried out. Twenty- four hours after the last treatment regimen, rats were euthanized by placing them in desiccator with chloroform soaked cotton wool. Blood samples were collected via cardiac puncture in the heparinized tubes and then centrifuged at 1500 rpm for 10 minutes. Brain samples were excised, then rinsed in PBS and homogenized over ice in 0.1 M cold sodium phosphate buffer(pH 7.4). The homogenate was centrifuged at 4^{o}C for 10 minutes at 10,000 rpm. The supernatant obtained was aliquot for subsequent biochemical analysis.

2.4 Behavioural assessments

On the 21st day of cadmium chloride or/ restraint stress conduction, behavioural assessment with Elevated plus maze and Y maze were performed.

Elevated plus maze Test

Elevated plus maze was used to measure anxinogenic behavior. The maze was built with two open and two closed arms enclosed with 30cm high walls, which is 10cm wide and mounted 50cm above the ground. Rats were placed at the junction of the open and closed arms, facing the open arm opposite to where the experimenter and their behavior (the number of entriesmade in the open) was recorded for six (6) minutes.The maze was cleaned with an alcoholic solution followed by wet and dry paper towels following each test (Guedri*et al*., 2017).

Y maze

Y maze was used to assess the state ofworkingmemory of the rats. The arm length of Y maze is about 40cm; arm bottom width is 3cm, arm upper width 13cm, height of the wall 15cm. Each rat was placed in the central area and the number of entriesinto the arms and alteration were recorded for 10 minutes. The working memory was calculated as number of spontaneous alterations/number of the total new arm entries(Yoshizak*et al*., 2020).

2.4 Biochemical Assays

Serotonin (SRO) andAcetylcholinerase (AchE) activities, wereassayed using commercial kits and standardized methods.

2.5 Statistical Analysis

SPSS (version 16.0) was used for all statistical analysis. All results obtained are expressed as Mean ± Standard Error of the Mean (SEM). Data were analyzed using one-way ANOVA and Duncan's posthoc testfor multiple comparisons. P value < 0.05 was considered to be statistically significant.

3.0 Results and Discussion

Results

Table 2: Effect of restraint stress and cadmium chloride administration on brain weight in female Wistar rats.

GROUP	CTL	RSS	CCC	RSC
Mean ± SEM	1.33±0.03[a]	1.48±0.12[a]	1.32±0.03[a]	1.20±0.06[a]

Values are expressed as mean ±SEM (n= 6). Groups with superscript of different letters are significantly ($p<0.05$) different from each other. Groups with superscript of same letters are not significantly different from each other.

In female Wistar rats exposed to cadmium chloride and restraint stress, there was no significant difference across all groups.

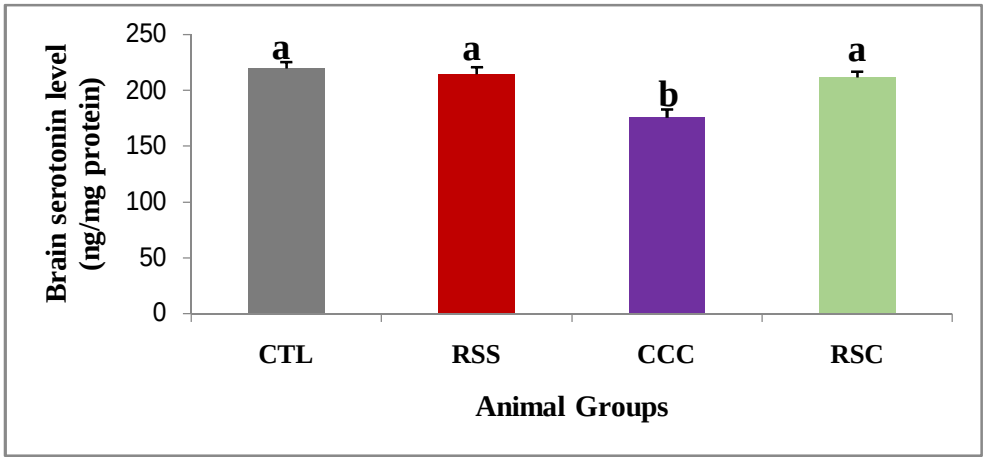

Figure 1: Effect of restraint stress and cadmium chloride administration on brain serotonin in female Wistar rats.

Values are expressed as mean ±SEM (n= 6). Groups with superscript of different letters are significantly ($p<0.05$) different from each other. Groups with superscript of same letters are not significantly different from each other.

Result showed that there was significant ($p<0.05$) decrease in brain serotonin in CCC group when compared to CTL. There was no significant difference in RSS when compared to CTL. There was no statistical significant difference in RSC when compared to RSC and CCC.

Table 3: Effect of restraint stress and cadmium chloride administration on cerebral acetylcholine esterasein female Wistar rats.

GROUP (µmol/gtissue)	CTL	RSS	CCC	RSC
Mean ± SEM	0.05 ± 0.003^{a}	0.06 ± 0.007^{a}	0.08 ± 0.003^{a}	0.14 ± 0.009^{b}

Values are expressed as mean ±SEM (n= 6). Groups with superscript of different letters are significantly ($p<0.05$) different from each other. Groups with superscript of same letters are not significantly different from each other.

There was significant ($p<0.05$) increase in acetylcholine esterasein RSC group when compared to RSS and CCC. There was no significant difference in RSS and CCC when compared to CTL.

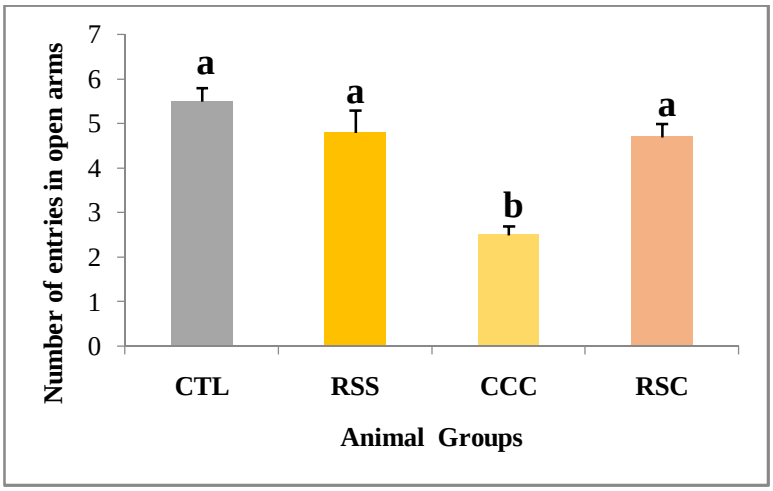

Figure 2: Effect of restraint stress and cadmium chloride administration on number of entries in open arms of an Elevated Plus Mazein female Wistar rats.

Values are expressed as mean ±SEM (n= 6). Groups with superscript of different letters are significantly ($p<0.05$) different from each other. Groups with superscript of same letters are not significantly different from each other.

There was significant ($p<0.05$) decrease in the numbers of entities in open arms in CCC group when compared to CTL. However there was no significant difference in RSS when compared to CTL. Also there was no significant difference in RSC when compared to RSS and CCC.

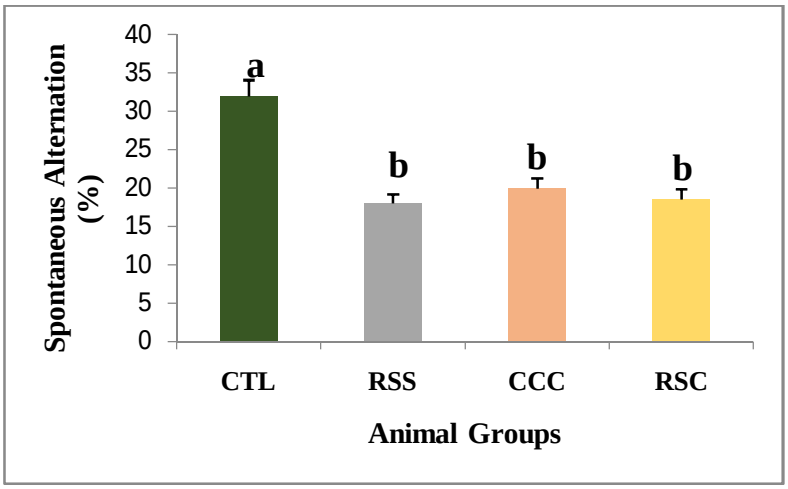

Figure 3: Effect of restraint stress and cadmium chloride administration on spontaneous alteration (Y maze) in female Wistar rats.

Values are expressed as mean ±SEM (n= 6). Groups with superscript of different letters are significantly ($p<0.05$) different from each other. Groups with superscript of same letters are not significantly different from each other.

There was significant ($p<0.05$) decrease in spontaneous alteration in RSS, CCC, and RSC group when compared to CTL. However there was no significant difference in RSC when compared to RSS and CCC.

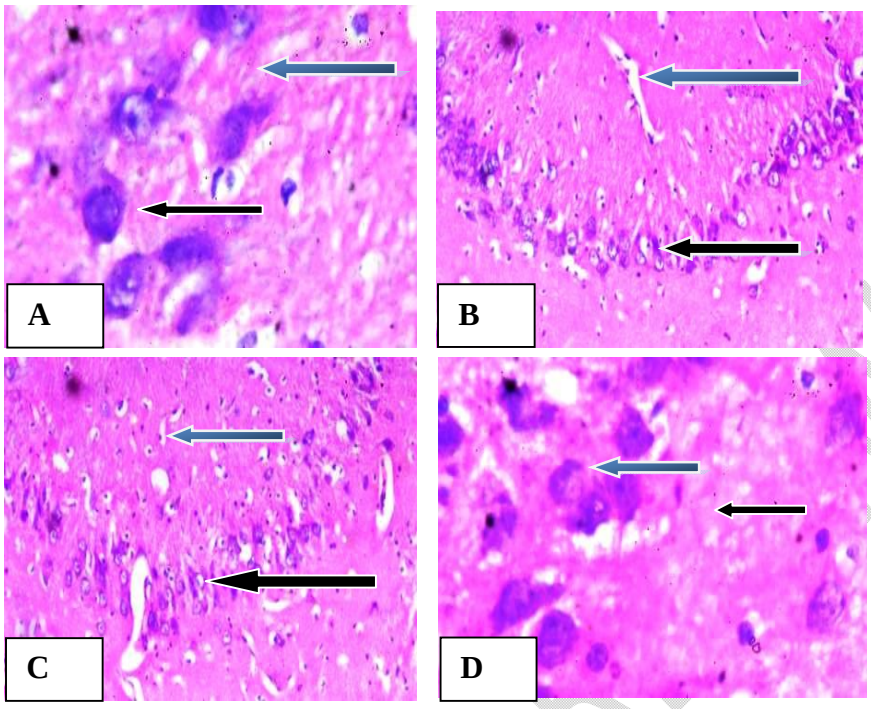

Figure 4: Effect of cadmium chloride administration and restraint stress on hippocampal histology

Haematoxylin and Eosin stained micrographs of the hippocampus of control and experimental rats. Histological sections of CTL rats (A) and CCC rats (B) showed a normal structural architecture (blue arrow) with normal neuronal cells (black arrow) while in the RSS (C) rats the hippocampus is fat filled with degenerated neuronal cells (black arrow) and poor structural organization (blue arrow). In the RSC (D), hippocampus with depleted neuronal cells (black arrow) and disorganized structural organization (blue arrow) was seen (H & E, ×400).

Discussion

The toxicological effects of cadmium on the nervous system in both in vitro and in vivo has been shown extensively inprevious studies (Oh *et al*., 2018; Suburaja*et al*., 2024). The brain is one of the organs vulnerable to cadmium toxicity (Arruebarrena *et al*., 2023). The hippocampus is the major organ associated with mood and cognition. Chronic stress has detrimental impact on cogntion (McEwen,2017). Organ weight changes are key indicators of toxin induced organ damage (Lazic and semenova, 2020). In this study, the brain weight showed no significant difference across all groups. Result observed in

restraint stress alone group could be due to integrated stress response (ISR), a cellular defense mechanism that functions to help cells adapt to acute stress by modulating protein synthesis (Lawrence *et al.,* 2024). ISR pathway also plays a crucial role in synaptic plasticity, learning and memory (Helseth et al., 2021). The combined effectsof cadmium and restraint stress exposure did not have significant effect on brain weight, indicating that the study might have been conducted over a short duration for a significant change to be observed. Serotonin is one of the major monoamine neurotransmitters involved in learning and memory consolidation. In fig. 1, resultsobserved in the cadmium only group is consistent with previous study of Ojo *et al.*(2023), where there was significant ($p<0.05$) decrease in brain serotonin following cadmium exposure when compared to control. Reduction in serotonin level leads to disruption in memory consolidation (Coray and Quednow*et al*., 2022). Decrease in serotonin level may be due to disruption in tryptophan hydroxylase, an enzyme that plays a crucial role in converting tryptophan to serotonin (5-HT), resulting to decreased serotonin synthesis (Rasha *et al*., 2015). In the restraint stress alone group, there was relative decrease in serotonin level when compared to control group. This result is partially in-linewith the study of Oh *et al*. (2018) who reported that restraint stress significantly ($p<0.05$) decreasedserotonin level indicating that, elevation in stress hormone level as a result of hyperactivation of hypothalamic pituitary adrenal (HPA) axis can disrupt the catecholaminergic and monoaminergic systems leading to a reduction in serotonin level. The study observed the combination of restraintstress and cadmium when compared to cadmium and restraint stress alone group showed no significant difference in serotonin level suggests that the level serotonin might have been reduced to a threshold by either cadmium alone or stress alone.

Acetylcholinesterase (AChE) is an enzyme known to play a major roleincholinergic neurotransmission. It hydrolyzedacetylcholine (a neurotransmitter involved in memory process) in the synaptic cleft of cholinergic synapses and neuromuscular junction. Cadmium toxicity has been implicated in cholinergic neurotransmission disruption (Gupta et al., 2017). In table 3, the result observed in the cadmium and restraint stress showed a significant ($p<0.05$) increase in acetylcholinesterase level when compared to the cadmium alone and restraint stress alone. The combination of cadmium and stress resulted in an increase in acetylcholinesterase level signifying a decrease in acetylcholine.The decrease in acetylcholine disrupts cholinergic signaling, which affect synaptic plasticity and result in cognitive deficit.

According to this study, in fig 2 there was significant ($p<0.05$) decrease in number of entries in open arm of elevated plus maze in cadmium alone group when compared to control group, this is consistent with the previous study of Adeniyi *et al*., 2014. Decrease in the number of entries in open arm suggests an increase in anxiety level. The neurotoxic effect of cadmium can resultsin depletion in serotonin level leading to alteration in neurotransmission, as serotonin is a key modulator in anxiety regulation.The combined effect of cadmium and stress showed no statistical significant difference in the restraint stress and cadmium chloride group when compared to the cadmium and restraint stress alone group. However, histological evaluation showed neuronal apoptosis and altered structural organization indicating that if the study had been carried out for a longer duration significant changes might have been observed. Also, this could be as a result of the rats adapting to stress, thereby reducing anxiogenic behavior. This suggests that adaptation to stress might have reduced the synergetic effect of cadmium when combined with restraint stresscausing a reduction in anxiety-likebehavior.

Spontaneous alteration depends on the natural ability of an animal to explore the novel arm of the Y maze rather than revisiting the previously explored arm. In fig 3, the observed statistical significant ($p<0.05$) decrease in spontaneous alteration in restraint stress alone group when compared to the control groupis consistent with the previous studies of Amin et al. (2015) and Thongrong et al. (2023), suggesting that hyperactivation of the HPA axis as a result of stress could have induced hippocampal degeneration and neuronal apoptosis which result in learning and memory impairment.Result observed in the cadmium alone group is consistent with the findings of Lamtai*et al*. (2021) where spontaneous alteration were significantly decrease following cadmium intoxication in treated groups when compared to their relative controls. Cadmium interferes with serotoninergic system resulting in spatial working memory impairment this is evident in result observed in the brain serotonin level. The combined effect of cadmium and stressshowed no significant difference in spontaneous alteration when compared to cadmium alone group and restraint stress alone group. This suggests that the individual effect of cadmium or stress might have decrease the spontaneous alteration to a threshold in which the combination of cadmium and stress may not cause further impairment in cognitive behavior this could be attributed to converging mechanism of cadmium and stress.

In this present work, examination of section of hippocampus, by light microscope, did not show notable differences among rats in control and cadmium alone group. On the other hand, Restraint stress induced histological changes in the structural organization and neuronal cell degeneration. This is consistent with the findings of Elfakharany et al, 2024. Furthermore, the neurotoxic effects of cadmium and restraint stress wereevident in the altered morphological structure and neuronal depletion of the hippocampus.

4.0 CONCLUSION

In this study, Cadmium exposure and restraint stressaltered neurotransmission, increased anxiety-like behavior, decreasedcognitive abilities, increasedalteration inhippocampal architecture, increasedneuronal degeneration and depletion as revealed in the histological evaluation resulting in cognitive deficits. Continuous bioavailability to cadmium poses threat globally due to increasedenvironmental pollution and increase in psychological stress intensified by soico-economic crisis, academic and worked-related demand and other environmental factor.

DISCLAMIER (ARTIFICAL INTELLIGENCE)

I hereby declare that NO generative AI technologies such as large language models (Chatgpt, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscript.

INSTITUTIONAL REVIEW BOARD STATEMENT

This study was conducted following the Institutional Animal Care and Use Committee (IACUC) guidelines, in strict compliance with the National Institutes of Health (NIH) guideline for the care and use of laboratory animals.

INFORMED CONSENT STATEMENT

Not applicable

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