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Original Article

Progesterone modulates cadmium-induced oxidative stress and inflammation in hepatic tissues of Wistar rats

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Abstract: In recent times, there has been an increased risk of human exposure to cadmium especially in developing countries. We studied the role of progesterone as an anti-inflammatory and antioxidant agent in cadmium induced toxicity. Cadmium toxicity was induced with cadmium chloride (30 mg/kg) per oral while the control group was given distilled water. The Cd group was given $CdCl_2$ only, P_4 group; progesterone only (10 mg/kg intraperitoneally) and Cd+P_4 group; $CdCl_2$ and progesterone. All treatments lasted for 21 days. Following sacrifice, liver function tests and antioxidant status were assessed using standard kits; TNFα was immunolocalized across the study groups and the staining intensity measured using Image J software. Cadmium administration induced oxidative stress by a significant elevation in MDA and GC6P levels and a significant reduction in SOD, CAT, and GSH. These were attenuated by progesterone administration. While cadmium exposure caused an increase in serum ALT, AST, and ALP activities, progesterone significantly alleviated these effects. Inflammation shown by significant immunoreactivity in the TNFα positive cells in the liver in the cadmium group was reversed by progesterone. We conclude that cadmium toxicity induces oxidative stress that was attenuated by progesterone.

Keywords: Progesterone, TNFα, cadmium toxicity, liver, oxidative stress, inflammation

Introduction

Cadmium (Cd) is a ubiquitous environmental contaminant categorized as class I carcinogen with consequential health implications [1, 2]. Although it is usually present at low levels in the environment, human activities have greatly increased its levels in environmental media relevant to population exposure. The toxic effects and biologic roles of Cd on the health of humans have attracted much attention due to its persistent increase and presence in the environment. Cadmium gets into the food chain from the soil, where it gets transferred to plants, posing a hazard for animals and humans [3]. Depending on the exposure time and dose, the toxic effects of Cd on various organs including the liver, brain, and kidneys are due to the delay in elimination from the body and a prolonged life span in organisms [4]. The comprehensive mechanisms fundamental to the destructive consequence of exposure to Cd on various organs of the body have not been fully explained, although oxidative stress induced by reactive oxygen species (ROS) has been recognised as one of the important mechanisms [5]. Studies have suggested that Cd toxicity is largely caused by oxidative stress [6, 7] which is indirectly induced by increasing ROS production, such as singlet oxygen (O_2), superoxide radical, hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH) [8, 9]. Consequently, there is a reduction in antioxidant proteins such as superoxide dismutase, catalase, and glutathione reductase [10]. Oxidative stress has been reported to be one of the major causes of organ damage resulting from Cd toxicity [11, 12]. Cadmium has been shown to induce neurotoxicity and hepatocellular damage and adversely affects the biologic function of the liver [13-15]. According to Yamano et al. [16] acute hepatotoxicity resulting in endothelial cell injury occurs as a result of a toxic effect and ischemia. Following these, inflammatory insult occurs

with the activation of Kupffer cells and the infiltration of neutrophils accompanied by upregulation in the activity of inflammatory mediators. In the brain, Cd-induced neuronal damage occurs through amplifying the formation of ROS, which leads to oxidative stress and reducing the antioxidant defense mechanism, thus resulting in neurodegeneration and defects in memory [17]. Additionally, Cd represses the base excision repair enzymes, important for restoring DNA insults as a result of oxidative stress [18]. Cadmium exposure has also been shown to result in its accumulation within the liver and hepatocellular damage [19].

Progesterone is a steroid hormone with potent anti-inflammatory and antioxidant properties [20, 21]. Despite its original concept as a progestational hormone, it has been described as having antioxidant, anti-apoptotic, and anti-inflammatory potentials [22, 23]. It also exerts neuroprotective effects in experimental brain insults [20, 21]. According to Roof and Hall [24], progesterone reduces the damage caused by lipid peroxidation through its membrane-stabilizing effect and also suppressing neuronal hyperexcitability. Progesterone supplementation has also been recorded to protect against oxidative stress in the liver of ovariectomized pinealectomized rats, protecting it against lipid peroxidation [25]. Apart from its antioxidant properties, clinical findings have shown an anti-inflammatory role of progesterone [26]. Progesterone has inhibitory effects on the inflammatory response; it has been shown to decrease inflammatory cytokine expression such as TNF-α and IL-1β in brain-injured rats [27]. Pre-treatment with progesterone has been shown to control inflammation by decreasing the inflammatory tumor necrosis factor α (TNF α) [28].

Given the significant antioxidant and anti-inflammatory effects of progesterone, the present study was carried out to investigate its hepatoprotective effects; especially in regulating oxidative stress and inflammation associated with Cd toxicity.

Material and methods

Animal care and management

All animals were handled in compliance with the Guide for the Care and Use of Laboratory Animals [29]. Following ethical institutional approval (UNIOSUNHREC/2018/005), twenty adult male rats with average weight of 135 g, obtained from the animal holding of the College of Medicine, Ekiti State University, Ado-Ekiti, Nigeria were used for this study. They were reared under standard laboratory conditions in the animal house and given free access to rat feed and water throughout the study.

The rats were randomly distributed into 4 groups of 5 animals each and housed in polyethylene cages with wire mesh lid. The protocol of treatment was as follows: Control group was given distilled water p.o., Cd group was given Cadmium chloride ($CdCl_2$) only (30 mg/kg p.o.), P_4 group was given Progesterone only (10 mg/kg in DMSO i.p.) while the Cd+P_4 group received Cadmium chloride (30 mg/kg p.o.) then Progesterone (10 mg/kg b.w. in DMSO i.p) 30 minutes later. $CdCl_2$ was dissolved in distilled water. All treatment lasted for 21 days.

Prior to sacrificing the rats, physical observations including survival rate, physical appearance, and changes in body weight were made.

At the end of the experimental period, the rats were sacrificed by exposure to ether vapor. Following a mid-line cut in the anterior abdominal wall, the livers of the rats were excised and the portions meant for the localization of TNF-α were fixed in 10% neutral buffered formalin while the those used for biochemical analyses were transferred in ice to a centrifuge bottle.

Antioxidant status and liver function tests

The tissues were homogenized in 10% w/v homogenizing buffer in a Teflon glass homogenizer. The samples were centrifuged at 10,000 rpm at 4°C for 15 min. The supernatant aliquots were utilized for the determination of liver function tests (Alanine transaminase, Aspartate transaminase, Alkaline phosphatase, Bilirubin and Total protein) and oxidative stress markers including glucose-6-phosphate dehydrogenase, glutathione, superoxide dismutase, catalase and malondialdehyde using standard procedures.

Immunoenzymatic detection of TNF-α expressing cells and staining for immunoreactivity

The tissues were dehydrated and processed by routine methods. Thin sections made using a

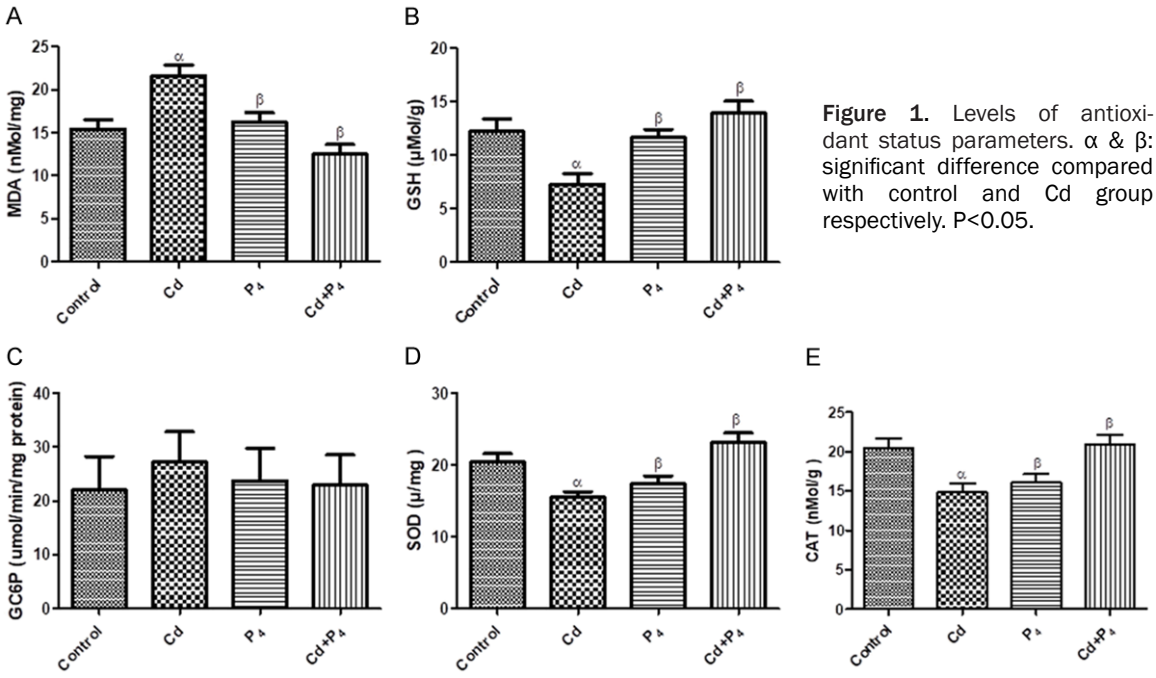

Figure 1. Levels of antioxidant status parameters. α & β: significant difference compared with control and Cd group respectively. P<0.05.

Rotary microtome were transferred onto poly-L-lysine coated glass slides (X-tra Adhesive, Leica Microsysytems, Germany). Sections were dewaxed in xylene, rehydrated and incubated in a Target Retrieval Solution (Dako, Denmark) and then 3% hydrogen peroxide (H_2O_2) for 10 min for endogenous peroxidase blocking. This was followed by thorough rinsing with PBS and incubation with normal goat serum for 30 minutes. Thereafter, sections were incubated for 30 min in anti-TNFα polyclonal antibody (Elabscience, USA) using a dilution ratio of 1:50 at room temperature. Sections were then rinsed with wash buffer and incubated with anti-rabbit secondary antibodies (HRP) (Dako, Denmark) for 20 min at room temperature prior to visualisation with diamino-benzidine (DAB) (Elabscience, USA). Mayer's haematoxylin was used to counterstain the nuclei while the primary antibody was replaced with wash buffer for negative controls.

Morphometric evaluation of the immunostained sections

The stained sections were examined and captured at different magnifications under OMAX 40X-2000X digital light microscope. Image Analysis was done using Image J software of the National Institute of Health (USA). Using the immunoratio plugin, the areas of DAB brown staining were automatically selected from haematoxylin counter-stained blue nuclear area. Since the DAB area signifies positive immunoreactivity, the plugin generates the percentage of DAB area to the whole nuclear area.

Data analyses

Results are presented as means ± SEM. One-way analysis of variance was used for comparative analysis of the data between treated and non-treated groups of rats while Bonferroni test for comparison across groups. A $p<0.05$ was considered significant. Statistical analysis was done using GraphPad Prism version 5.00 (San Diego, USA).

Results

Antioxidant status

As seen in **Figure 1**, there was a significant difference in the tissue expression of MDA ($p=0.0004$), GSH ($p=0.0025$), SOD ($p=0.0008$) and CAT ($p=0.0028$) across the groups; however, there was no significant difference in the levels of GC6P across the study groups ($p=0.9303$). While there was a significant ($p<0.0001$) elevation in the expression of MDA in the Cd group of rats compared with the control, the observed increase in the level of GC6P in the Cd group compared with the control was

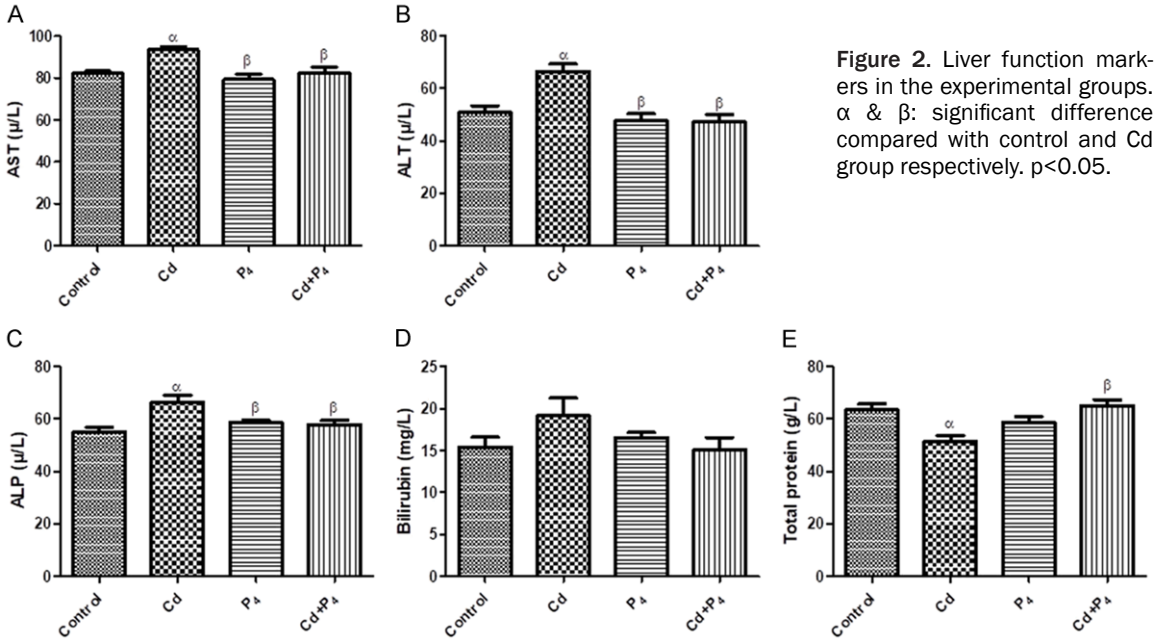

Figure 2. Liver function markers in the experimental groups. α & β: significant difference compared with control and Cd group respectively. p<0.05.

not statistically significant (p>0.0001). Also, a significant decrease was observed in the GSH, SOD, and CAT levels in the Cd group compared with the control (p<0.0001). However, the elevation in the expression of MDA and GC6P in the Cd group was reduced in both the P_4 and the Cd+P_4 groups albeit significantly in MDA alone (p<0.0001) (**Figure 1A** and **1C**). Likewise, a significant increase in the levels of GSH, SOD, and CAT was seen in the Cd+P_4 group compared with the untreated Cd group (p<0.0001) (**Figure 1B**, **1D** and **1E**).

Liver function markers

From **Figure 2A**, a significant difference was observed in the expression of AST (p=0.0010), ALT (p=0.0003), ALP (p=0.0285) and total protein (p<0.05) while there was no significant difference in the levels of bilirubin (p=0.2235) across the groups. While a significant elevation was observed in the tissue level of AST, ALT, and ALP in the Cd group compared with the controls (p<0.0001); the level of bilirubin was also increased but it was not significant (p>0.05); and there was a significant reduction in the total protein levels in the Cd group compared with the control. Treatment with progesterone significantly reversed these, as there was a significant reduction in the levels of AST, ALT and ALP; however, the level of bilirubin was elevated but not significantly increased (p>0.001) while the level of total protein was significantly increased (p<0.0001).

Immunolocalization and morphometric image analysis of TNFα in the liver

Figure 3A shows the immunoreactivity of TNFα in the liver tissues of rats across the study groups. There was little or no staining in the control and P_4 groups. There was a significant immunoreactivity in the Cd group indicative of inflammation, but a reduced intensity of staining was observed in the Cd+P_4 group. As seen in **Figure 3B**, there was a significant difference in immunoreactivity of TNFα in the hepatic tissues of the rats across the study group (p=0.0001). A significant increase in immunoreactivity of cells was observed in Cd group compared with the both the control and P_4 groups respectively (p<0.05). However, restorative effects were observed in the Cd+P_4 group with a significant reduction in the immunoreactivity of the hepatocytes compared with the Cd group (p<0.05).

Discussion

One of the mechanisms underlying the toxicity of cadmium is the induction of oxidative stress, resulting from the production of reactive oxygen species and exhaustion of the antioxidant defense complex. Studies conducted on cad-

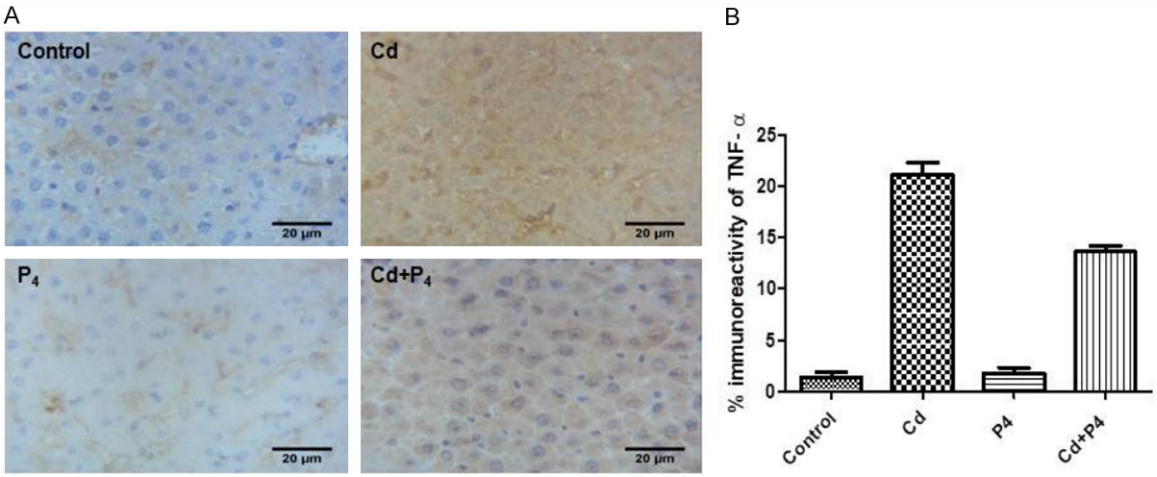

Figure 3. A. Immunohistochemical study of TNF-α in the liver tissue sections. Areas of brown staining indicate immunoreactivity in the hepatocytes and central vein of rats in the experimental groups. B. ImmunoRatio Image J Plugin measuring the percentage of positively stained nuclear area. *p < 0.05.

mium provide robust proof, confirming one of the important mechanisms of Cd toxicity as an oxidative stress, with the liver as a vital organ of acute exposure [30]. The induction of oxidative stress caused by cadmium is accomplished by two independent but related mechanisms [31]. The first mechanism entails the production of ROS, i.e. superoxide (O_2-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH); the second mechanism involves exhaustion of the cells' major antioxidants resulting in enzymatic damage and ROS accumulation [32]. In our study, cadmium increased lipid peroxidation, evident from an increase in malondialdehyde which is one of the products of polyunsaturated fatty acids peroxidation in the cells; this indicates a role of cadmium in increasing free radicals. Gehan and Ayman [33] suggested that lipid peroxidation in the liver soon after Cadmium exposure occurs by displacement of copper and iron from within the cell and subsequent initiation of the Fenton reaction. Although progesterone lacks a classic antioxidant chemical composition, it has been shown to have a protective role against the damage caused by free radicals [34]. Also, Vedder et al. [35] have shown that administration of progesterone reduces oxidative stress which results in cellular changes, in a dose-dependent manner. Results from our work show that progesterone inhibits liver lipid peroxidation, due to the fact that it was able to reduce the production of malondialdehyde in progesterone-treated rats exposed to cadmium similar to those found in the controls. This result agrees with Benlloch-Navarro et al. [36] who in their study, observed that progesterone administration was able to reduce retinal malondialdehyde concentrations in rd10 mice, suggesting its therapeutic value in the management of retinal diseases associated with lipid peroxidation. Contrary to this, Verma and Rana [37] studied the impact of progesterone with regard to the metabolism of benzene by lipid peroxidation and found that benzene-treated ovariectomised rats administered progesterone, resulting in exacerbated lipid peroxidation in the kidneys and liver. These researchers suggested that the pronounced levels of lipid peroxidation probably manifested because of the lengthy duration between progesterone treatment and ovariectomy [37].

Superoxide dismutase (SOD) and catalase (CAT) are crucial for maintaining ROS levels in organisms and also as biologic markers to show ROS production [38, 39]. Studies have shown that oxidative stress results from cadmium induction, thereby altering the activity of SOD and CAT. In this present study, cadmium administration resulted in reduced activity of both CAT and SOD possibly by interacting with the enzyme molecules. This result is in line with studies by Hussain et al. [40] and Casalino et al. [41]; in these studies, SOD activity was impeded by cadmium both in vitro and in vivo in the rat liver. Similarly, Shi et al. [42] studied SOD and CAT activity in Carassius auratus liver and concluded that CAT activity was inhibited

by cadmium while increasing the activity of SOD. Treatment with progesterone increased the levels of antioxidant enzymes, showing an increase in activity of enzymes against cadmium induced oxidative stress. Pajovi et al. [43] reported the efficacy of progesterone in increasing expression of antioxidant enzymes such as SOD. The improvement in antioxidant enzyme levels to significant values observed in our study suggests the free radical scavenging and antioxidant actions of progesterone in Cd induced oxidative stress. This agrees with the work of Aggarwal et al. [44], who studied the possible neuroprotective effect of progesterone on a mouse model of cerebral ischaemia. Progesterone was able to increase the antioxidant enzymes such as SOD, GPx, and catalase after a significant decrease in the antioxidant enzymes. Other authors have also demonstrated cadmium-induced alterations in the brain parenchyma and neurons leading to encephalopathy, peripheral neuropathy, and memory deficits [45, 46].

Once cadmium enters the cells and generates excess ROS, the antioxidant defense mechanism is triggered [30]. Glutathione (GSH), a low molecular weight antioxidant synthesized in cells, maintains redox homeostasis either by direct union with cadmium or by reducing levels of free radicals [47, 48]. In this present study, cadmium resulted in the reduction of GSH levels while progesterone was able to bring about a significant restoration. Our study result is in line with Sánchez-Vallejo et al. [49] who showed the multiple benefits of progesterone which included the increase in GSH concentration.

To ascertain the effect of cadmium on liver function, we analysed the actions of ALT and AST alongside ALP and bilirubin, markers of hepatic injury. Cadmium exposure caused an increase in ALT, AST, and ALP activities in the tissues; and treatment with progesterone significantly mopped up cadmium-induced damage to the liver by reducing ALT, AST, and ALP levels.

Inappropriate production of TNFα or sustained activation of its signalling are associated with infectious and inflammatory conditions [50, 51] and serum levels correspond with degree of infectiousness [52]. It induces ROS production, lipid peroxidation, depletion of antioxidant enzymes, and derangement of mitochondrial membrane potential [53]. In this study, morphometric image analysis of TNFα in the liver also showed elevated immunoreactivity with TNFα in the Cd group and progesterone reversed this effect. Several studies have demonstrated the potent anti-inflammatory properties of progesterone [20, 54]. Results from our study corroborated that of Aggarwal et al. [44] who reported reduction in the levels of TNFα following progesterone treatment in opposing the vascular complications occurring during the acute phase of ischemic stroke.

Conclusion

This study has reinforced the hypothesis that progesterone is a candidate for the management of cadmium-induced oxidative stress and its attendant inflammatory changes. Thus, progesterone is a therapeutic option in the treatment of diseases associated with inflammation and generation of free radicals. However, more studies need to be done to validate the exact mechanism of action.

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Disclosure of conflict of interest

None.

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