Journal of
Environmental & Analytical Toxicology
ISSN: 2161-0525

Abbassy et al., J Environ Anal Toxicol 2014, 4:4
DOI: 10.4172/2161-0525.1000218

Research Article

Open Access

Impact of Oxidative Stress and Lipid Peroxidation Induced by Lambda-cyhalothrin on P_{450} in Male Rats: The Ameliorating Effect of Zinc

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Abstract

The present study was designed to investigate the effect of lambda-cyhalothrin (LCH) on lipid peroxidation, oxidative stress biomarkers and the activity of Cytochrome P_{450} in male rats and the protective role of zinc. LCH was administrated orally to rats at dose 2.6 mg/kg b.wt. (Which represents 1/10 LD_{50}) with 3 doses per week for 6 weeks (dose period). Rats were divided into four groups, eight rats for, each: (I) control group, (II) zinc group (Zn dose 227 mg/l in drinking water), (III) LCH-treated groups and LCH-Zn group (IV) as in group II and III. The present results demonstrated that LCH induced significant alteration in the activity of antioxidant enzymes (superoxide dismutase, SOD; catalase, CAT; glutathione-s-transferase, GST; glutathione peroxidase, GPx), glutathione reduced (GSH) and lipid peroxidation (LPO) levels and decreased cytochrome P_{450} (P_{450}) activity in plasma of male rats. In contrast, zinc-LCH treatment showed insignificant difference, compared to control results, regarding LPO, GST, CAT and P_{450}. LCH induced oxidative stress, lipid peroxidation and reduced P_{450} activity in the plasma of male rats. The overall results reveal the pronounced ameliorating effect of zinc in LCH-intoxicated rats.

Keywords: Lambda-cyhalothrin; Lipid peroxidation; Antioxidants enzymes; P_{450}; Zinc; Rat

Introduction

Synthetic pyrethroids are a diverse class of more than thousand powerful broad spectrum insecticides that are environmentally compatible by virtue of their moderate persistence, low volatility and poor aqueous mobility in soil [1]. They represent approximately one-fourth of the worldwide insecticides market [2]. Lambda-cyhalothrin (cyano-3-phenoxybenzyl-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropane carboxylate) is one of the newer synthetic type II pyrethroid insecticides [3] with effective and persistent activity against a large variety of arthropods harmful both to human and animal health, and to vegetal production [4]. Consistent with its lipophilic nature [5] pyrethroid insecticide such as lambda-cyhalothrin has been found to accumulate in biologicalmembranes leading to oxidative damage. It has been suggested that some effects directly related to pesticide toxicity could be due to changes in membrane fluidity [6,7], in lipid composition [8] and inhibition of enzyme activities [9-11].

In fact, reactive oxygen species (ROS) are produced by univalent reduction of dioxygen to superoxide anion (O^{-2}), which in turn disproportionate to H_2O_2 and O_2 spontaneously or through a reaction catalyzed by superoxide dismutase (SOD). Endogenous H_2O_2 may be converted to H_2O either by catalase or glutathione peroxidase (GSH-Px). Otherwise, it may generate a highly reactive free hydroxyl radical (^{-}OH) via a Fenton reaction, which is responsible for oxidative damage. GSH-Px converts H_2O_2 or other lipid peroxides to water or hydroxyl lipids, and during this process glutathione (GSH) is converted to oxidized glutathione [12]. Antioxidants are defense against free radical and oxidative attacks. They act as free radical scavengers and slow down not only radical oxidation but also the accompanying damaging effects in the body [13]. Previous studies [10,11,14-16]reported that ROS were involved in the toxicity of various pesticides.

Zinc (Zn) is an essential trace element, is relatively nontoxic and is integral to several key functions in human metabolism [17,18]. Not only has Zn been identified as a component of key enzymes and regulatory proteins, it was recently suggested that the preventive effects of zinc may partly be mediated through increase in cytochrome P_{450} enzymes in subjects with alcoholic liver disease [19,20].

However, there is still a clear lack of understanding whether the toxic effects of lambda-cyhalothrin mediated through drug metabolizing enzymes, and further if zinc may have any preventive role in such toxic conditions. Therefore, the present study was designed to evaluate the protective potential effect of zinc on oxidative damage induced by lambda-cyhalothrin in male rats.

Materials and Methods

Chemicals and reagents

Lambda-cyhalothrin (Lambda EG®, EC %) was obtained from Arab Company for Chemical Industries Co., Egypt. Zinc sulfate ($ZnSO_4 \cdot 7H_2O$) was obtained from Merck (Germany). Kits of SOD, CAT, GST, GSH, GR and GPx were obtained from Bio-diagonistic, Dokki, Giza, Egypt. Kit of cytochrome P_{450} was obtained from Boehringer Mannheim Gmbh Diagonstics, Germany.All other chemicals were of reagent grades and obtained from the local scientific distributors in Egypt.

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Received February 20, 2014; **Accepted** April 16, 2014; **Published** April 18, 2014

Citation: Abbassy A, Marzouk MA, Mansour SA, Shaldam HA, Mossa ATH (2014) Impact of Oxidative Stress and Lipid Peroxidation Induced by Lambda-cyhalothrin on P_{450} in Male Rats: The Ameliorating Effect of Zinc. J Environ Anal Toxicol 4: 218. doi: 10.4172/2161-0525.1000218

Animals

Male albino rats weighing 120 ± 10 g were obtained from the Animal Breeding House of the National Research Centre **(NRC)**, Dokki, Cairo, Egypt, and were used in this study. The animals were housed in plastic cages and allowed to adjust to the new environment for a week before starting the experiment. Rats were fed on standard food pellets and tap water *ad libitum*. The rats were housed at 23 ± 2°C and in daily dark/light cycle. The experimental work on rats was performed with the approval of the Animal Care & Experimental Committee, college of agriculture in Damanhour, Egypt, and according to the guidance for care and use of laboratory animals [21].

Experimental design

Animals were divided into four groups, eight animals each as the following: Group I:Rats were served as control and given tap water. Group II: Rats were given zinc in drinking water dally at a concentration of 227 mg L^{-1} as Zn [22]. Group III: Rats were given LCH at a dose 2.6 mg/kg b.w, 1/10 LD_{50} [23] orally repeated dose day after day over period of 6 weeks (3 doses/week). Group IV: Rats were given LCH and Zn as descript in groups II and III. Animals were weighed weekly and the dose was adjusted accordingly.

Blood collection

At the end of exposure period, blood samples were withdrawn from the animals under ether anesthesia by puncturing the retro-orbital venous plexus of the animals with a fine sterilized glass capillary. Blood was collected into heparinized tubes and left for 20 min at room temperature, then centrifuged at 3000 rpm (600 g) for 10 minutes using BOECO model C 28, Germany, to separate the plasma. The plasma was kept in a deep freezer (-20°C) until analyzed within one week.

Oxidative stress biomarkers

Lipid peroxidation (LPO): Lipid peroxidation was estimated by measuring thiobarbituric acid reactive substances (TBARS) and was expressed in terms of malondialdehyde (MDA) content by a colorimetric method according to Satoh [24]. The MDA values were expressed as nmoles of MDA/ml.

Glutathione reduced (GSH): GSH was assessed spectrophotometrically according to the method of Goldberg and Spooner [25] using Boehringer Mannheim Gmbh Diagonstics kits. The method was based on Glutathione reductase catalysis the reduction of glutathione (GSSG) in the presence of NADPH. The GSH values were expressed as nmoles/ml.

Antioxidant enzymes: Superoxide dismutase (SOD, EC 1.15.1.1) activity was determined according to the method of Nishikimi *et al.* [26]. The method is based onthe ability of SOD enzyme to inhibit the phenazine methosulphate-mediated reduction of nitroblue tetrazolium dye.Briefly, 0.05 ml sample was mixed with 1.0 ml buffer (pH 8.5), 0.1 ml nitroblue tetrazolium (NBT) and 0.1 ml NADH. The reaction was initiated by adding 0.01 ml phenazine methosulphate (PMS), and then increased in absorbance was read at 560 nm for five minutes. SOD activity was expressed in μmol/ml.

Catalase (CAT, EC 1.11.1.6) activity was determined according to the method of Abei [27]. The method is based on the decomposition of H_2O_2 by catalase. The sample containing catalase is incubated in the presence of a known concentration of H_2O_2. After incubation for exactly one minute, the reaction is quenched with sodium azide. The amount of H_2O_2 remaining in the reaction mixture is then determined by the oxidative coupling reaction of 4-aminophenazone (4-aminoantipyrene, AAP) and 3,5-dichloro-2-hydroxybenzenesulfonic acid (DHBS) in the presence of H_2O_2 and catalyzed by horseradish peroxidase (HRP). The resulting quinoneimine dye (N-(4-antipyrl)-3-chloro-5-sulfonate-p-benzoquinonemonoimine) is measured at 510 nm. The catalase activity was expressed in μmol/ml.

Glutathione peroxidase (GPx; EC 1.8.1.7) was assessed spectrophotometrically according to the method of Paglia and Valentine [28] using Boehringer Mannheim Gmbh Diagonstics kits. The method was based on indirect measure of the activity of c-GPx. Oxidized glutathione (GSSG), produced upon reduction of organic peroxide by c-GPx, and is recycled to its reduced state by the enzyme glutathione reductase (GR). Results were expressed as μmol/ml.

Glutathione-s-transferase (GST; EC 2.5.1.13) activity was assessed spectrophotometrically according to the method of Habig *et al.* [29]. The method was based on the conjugation of 1-chloro-2 4-dinitrobenzene (CDNB) with reduced Glutathione (GSH) in a reaction catalyzed by GST. Increase in absorbance was monitored for 3 min at 30 sec intervals at wavelength of 340 nm. Results were expressed as μmol/ml.

Cytochrome P_{450}

Cytochrome P_{450} was determined according to the method of Masters *et al.* [30]. The method was based on the most common reaction catalyzed by cytochromes P_{450} is a monooxygenase reaction, e.g., insertion of one atom of oxygen into an organic substrate (RH) while the other oxygen atom is reduced to water. The function of the cytochrome P_{450} enzymes is to metabolize xenobiotic compounds with which an organism comes into contact. Results were expressed as nmoles/ml.

Spectrophotometric measurements

The spectrophotometric measurements were performed by using JENWAY 6305 UV-Vis spectrophotometer designed and manufactured in the U.K.

Statistical analysis

The results were expressed as mean ± S.D. All data were done with the Statistical Package for Social Sciences (SPSS 17.0 for windows). The results were analyzed using one way analysis of variance (ANOVA) followed by Duncan's test for comparison between different treatment groups. Statistical significance was set at p ≤ 0.05.

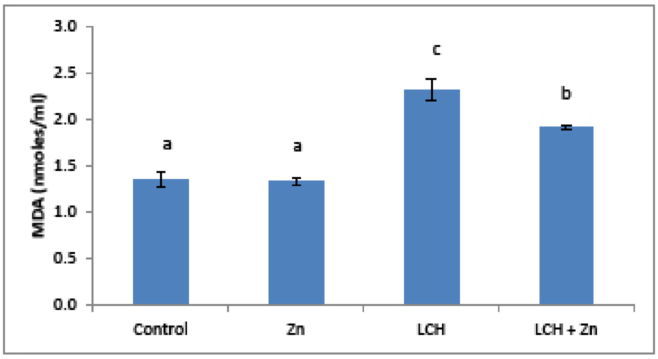

Figure 1: Effect of oral administration of lambda-cyhalothrin (LCH) on lipid peroxidation (LPO) in serum of male rats and the protective role of zinc (Zn). Bars represent the group means ± S.D; a,b,c & d values are not sharing superscripts letters (a,b,c & d) differ significantly at p ≤ 0.05.

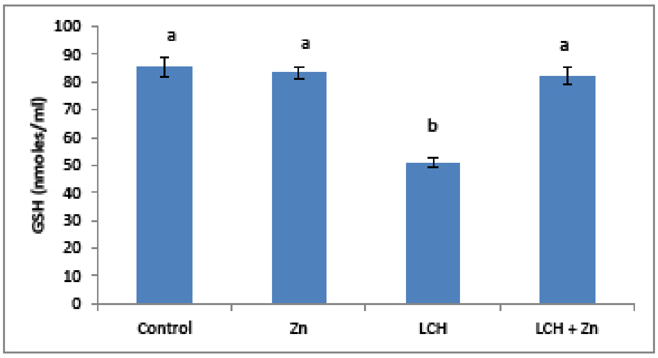

Figure 2: Effect of oral administration of lambda-cyhalothrin (LCH) onglutathione reduced(GSH) level in serum of male rats and the protective role of zinc (Zn). Bars represent the group means ± S.D; [a, b, c, d] values are not sharing superscripts letters (a,b,c & d) differ significantly at $p \leq 0.05$.

Results

Plasma MDA level was markedly increased by LCH administration as compared to control group (Figure 1). The difference between the two groups was statistically significant (2.32 nmoles of MDA/ml vs. 1.35 nmoles of MDA/ml, p ≤ 0.05). Co- administration of Zn to rats of LCH group alleviated lipid peroxidation induced by LCH in LCH-treatment and modulated significantly (1.92 nmoles of MDA/ml vs. 1.35 nmoles of MDA/ml, p ≤ 0.05) the levels of MDA in plasma compared to control. Results indicated that treatment with Zn produced a significant reduction in TBARS in LCH-treated rats; however Zn per se did not alter TBARS. As shown in Figure 2, significant decrease in GSH was observed after treatment of rats with LCH compared to control group (50.88 nmoles/ml vs. 85.37 nmoles/ ml). Co-administration of Zn with LCH modulated significantly the level of GSH to the normal control value (82.21 nmoles/ml vs. 85.37 nmoles/ml).

The effects of LCHtreatment on the activities of SOD, CAT, GPx and GST in plasma are shown in Figure 3. Activities of SOD (88.08 μmol/ml vs. 104.87 μmol/ml), GPx (0.76 μmol/ml vs. 0.87 μmol/ml) and GST (0.80 μmol/ml vs 1.07 μmol/ml) in plasma were significantly decreased (p ≤ 0.05), while CAT activity (0.69 μmol/ml vs. 0.48 μmol/ml) was significantly increased compared to control group. Co- administration of Zn with to rats caused significantly improvement the activities of CAT and GST in plasma compared with control values. The activity of SOD and GPx was returned to their control values in LCH+Zn-treated rats, while the decrease of GST and increase of CAT were significant (p ≤ 0.05) compared with LCH+Zn-treated group (Figure 3).

Plasma P_{450} activity was markedly decreased by LCH administration as compared to control group (Figure 4). The difference between the two groups was statistically significant (0.035 nmoles/ml vs. 0.136 nmoles/ml). Zn administered to rats of LCH+Zn group alleviated P_{450} activity induced by LCH treatment and modulated significantly (0.115 nmoles/ml vs.0.136 nmoles/ml, p ≤ 0.05) the activity of P_{450} in plasma compared to control. Results indicated that treatment with Zn produced a significant increase in P_{450} in LCH-treated rats.

Discussion

Free radicals have become an attractive means to explain the toxicity of numerous xenobiotics (e.g. pesticides) and some of these free radicals interact with various tissue components, resulting in dysfunction [10,14]. In fact, oxidative damage due to excessive production of reactive oxygen species (ROS) has been associated with defective organs dysfunction [14,31] and the inhibition of enzymes involved in free radical removal led to the accumulation of H_2O_2, which promoted lipid peroxidation and modulation of DNA, altered gene expression and cell death [32].

SOD, CAT and GPx are known to play an important role in

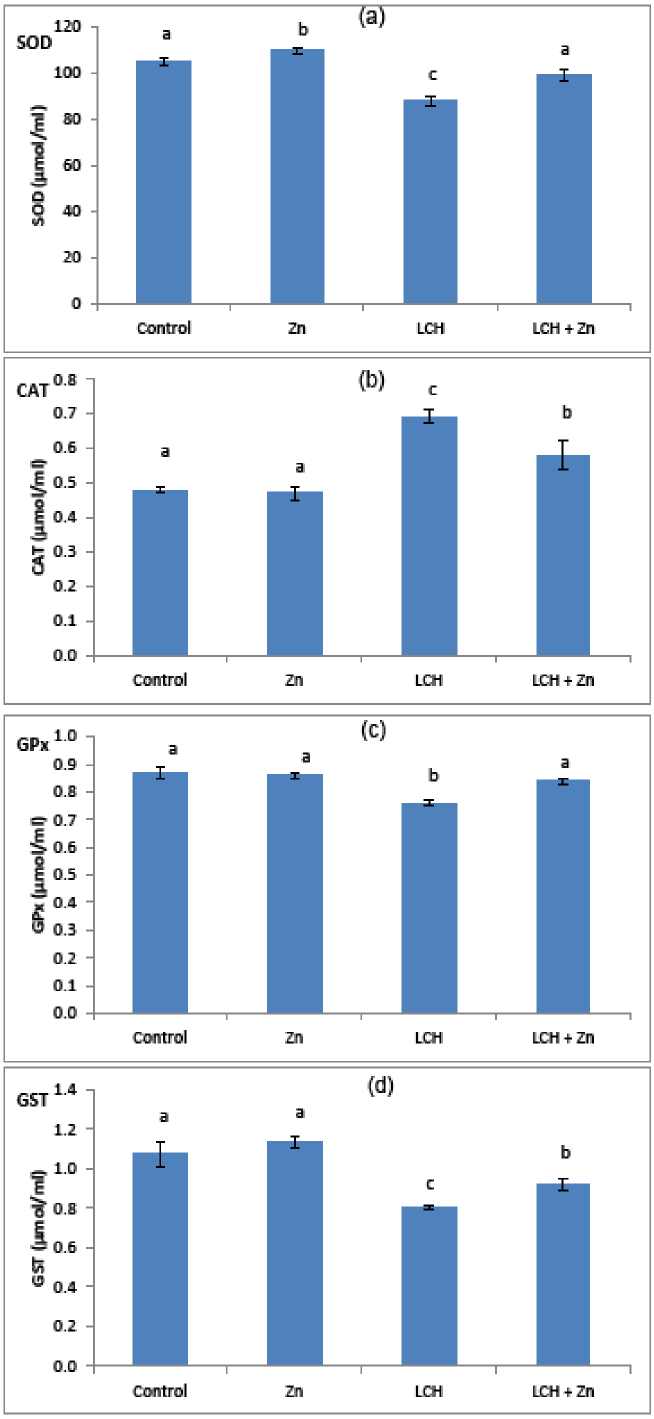

Figure 3: Effect of oral administration of lambda-cyhalothrin (LCH) on SOD, CAT,GPx and GST activity in serum of male rats and the protective role of zinc (Zn). Bars represent the group means ± S.D; [a, b, c, d] values are not sharing superscripts letters (a, b, c, d) differ significantly at $p \leq 0.05$.

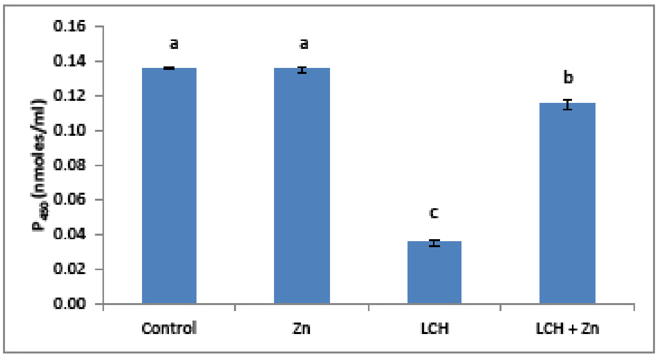

Figure 4: Effect of oral administration of lambda-cyhalothrin (LCH) on P_{450} activity in serum of male rats and the protective role of zinc (Zn). Bars represent the group means ± S.D., [a, b, c, d] values are not sharing superscripts letters (a,b,c & d) differ significantly at $p \leq 0.05$.

scavenging ROS. SOD catalyzes the destruction of the superoxide radicals to H_2O_2, while CAT together with GPx reduces the H_2O_2 into water and oxygen to prevent oxidative stress and in maintaining cell homeostasis. Also, GST is play essential role in the detoxification process. In the present study LCH induced significant decrease in the activity SOD, GPx and GST and increase in CAT activity in plasma of treated rats. So, the change in SOD, GPx, GST and CAT might be in response to increased oxidative stress. When a condition of oxidative stress strongly establishes, the defense capacities against ROS becomes insufficient [32], in turn ROS also affects the antioxidant defense mechanisms, reduces the intracellular concentration of GSH, lipid peroxidation and alter the activity of antioxidant enzymes e.g., SOD, CAT, GPx and GST. The changes in these oxidative stress biomarkers have been reported to be an indicator of tissue's ability to cope with oxidative stress [10,14,33]. ROS has also been known to decrease the detoxification system produced by GST [34]. Considering that GSTs are detoxifying enzymes that catalyze the conjugation of a variety of electrophilic substrates to the thiol group of GSH, producing less toxic forms [35], the significant decrease of GST activity in plasma of male rats after LCH administration may indicate insufficient detoxification of LCH in rat. Also, an important function of GST in response to oxidative stress is its ability to conjugate GSH with lipid peroxidation products [36]. Previous studies demonstrated that pyrethroids exposure altered antioxidant defense mechanisms and enhanced lipid peroxidation in rat liver [14,37-39], erythrocytes [37] and in fish [40]. Exposure of rats to a single dose of the pyrethroids, cypermethrin (25 µg kg^{-1}) and fenvalerate (4.5 µg kg^{-1}), lowered the activities of the antioxidant enzymes SOD and CAT, resulting in both lipid peroxidation and decreased levels of GSH in erythrocytes [41].

Lipid peroxidation has been suggested as one of the molecular mechanisms involved in pesticide-induced toxicity [10,11,14]. Malondialdehyde (MDA) level in LCH treatment was significantly higher than that in control. These indirectly suggest an increased production of oxygen free radicals in rats. Highly reactive oxygen metabolites, especially hydroxyl radicals, act on unsaturated fatty acids of phospholipid components of membranes to produce malondialdehyde, a lipid peroxidation product. Previous studies indicate that insecticides in both in vivo [10,11,42] and in vitro tests [43] alter the enzyme activities associated with antioxidant defense mechanisms.

Our results revealed that co-administration of zinc with LCH to treated animals retained the level of GSH and the activity SOD and GPx at the normal values. Catalase, CAT, GST activity and LOP level were improved, and such alterations were still significant in zinc-LCH-treated rats. The observed normalization trend of GSH, SOD and GPx following zinc treatment could possibly due to dismutation of O_2.- to H_2O which is catalyzed by SOD. Zinc is known to induce the production of metallothionein, which is very rich in cysteine, and is an excellent scavenger of ^{-}OH [44,45]. Also, the NADPH oxidases are a group of plasma membrane associated enzymes, which catalyze the production of $O_2.^{-}$ from oxygen by using NADPH as the electron donor. Zinc is an inhibitor of this enzyme [46].

Cytochrome P_{450} enzymes are essential for the metabolism and detoxification of many xenobiotics (e.g. pesticides). It has been reported that many chemicals (e.g. pesticides, drug) interactions are the result of an alteration of CYP_{450} metabolism [47]. In the current study, LCH decreased cytochrome P_{450} activity in LCH-treated rat. This may be due to the inhibition of heme synthesis and destruction of cytochrome P_{450} [48]. Previous studies showed that many pesticides have been reported to inhibit the activity and alteration in the expression of various cytochrome P_{450} isoforms (e.g. parathion, methomyl). These changes may increase the sensitivity of cells against reactive endogenous metabolites or other xenobiotics [49-51]. Co-administration of zinc to LCH-treated animals improved the activity of cytochrome P_{450} compared to LCH-treated rat. This change may due to the antioxidant role of zinc and alter the enzyme activities associated with antioxidant defense mechanisms.

Conclusion

The results of the present study demonstrated that exposure to LCH induced oxidative stress; lipid peroxidation and reduced P_{450} activity in the plasma of LCH- treated male rats. The overall results reveal the pronounced ameliorating effect of zinc in LCH-intoxicated rats.

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