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RESEARCH ARTICLE

OXIDATIVE STRESS INDUCED BY LAMBDA CYHALOTHRIN IN SELECTED TISSUES OF ALBINO MICE

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ABSTRACT

Pesticides are widely used in most sectors of the agricultural production to prevent or reduce losses by pests and thus can improve yield as well as quality of the produce, even in terms of cosmetic appeal, which is often important to consumers. Oxidative stress by increased production of reactive oxygen species (ROS) has been implicated in the toxicity of various pesticides. The present study was designed to investigate the induction of oxidative stress by Lambda cyhalothrin; a Type II pyrethroid in mice Intestine and Testis. Animals were divided into four equal groups; the first group used as control while groups 2, 3 and 4 were treated with sub lethal dose of Lambda cyhalothrin (4.8 mg/kg bw). Mice were daily administered with their respective doses for 30 days by gavage. Repeated oral administration of Lambda cyhalothrin was found to reduce the activities of the antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and level of reduced glutathione peroxidase (GP_X) and glutathione reductase GR. Intestine and Testis injury was confirmed by the histological changes. In conclusion, the oral sub-acute toxicity studies of Lambda revealed that this pyrethroid is of risk in albino mice.

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INTRODUCTION

Pesticides are widely used in agricultural production to prevent or control pests, diseases, weeds, and other plant pathogens in an effort to reduce or eliminate yield losses and maintain high product quality. Although pesticides are developed through very strict regulation processes to function with reasonable certainty and minimal impact on human health and the environment, serious concerns have been raised about health risks resulting from occupational exposure and from residues in food and drinking water. Occupational exposure to pesticides often occurs in the case of agricultural workers in open fields and greenhouses, workers in the pesticide industry, and exterminators of house pests. Pesticidal pollution bring about sudden and drastic changes in all the living organisms including pests and insects. By the toxicological studies the biological effects of pesticides and their mode of action are obtained (Ambika and Selvisabhanayakam, 2012). Exposure of the general population to pesticides occurs primarily through eating food and drinking water contaminated with pesticide residues, whereas substantial exposure can also occur in or around the home. Regarding the adverse effects on the environment (water, soil and air contamination from leaching, runoff, and spray drift, as well as the detrimental effects on wildlife, fish, plants, and other non-target organisms), many of these effects depend on the toxicity of the pesticide, the measures taken during its application, the dosage applied, the adsorption on soil colloids, the weather conditions prevailing after application, and how long the pesticide persists in the environment. Synthetic pyrethroid insecticidesare now being substituted for pest control and increased production (Muthuviveganandavel *et al.,* 2008). Lambda-cyhalothrin is a synthetic pyrethroid insecticide used worldwide in agriculture, home pest control, protection of foodstuff and disease vector control. The objective of this study was to investigate the propensity of Lambda-cyhalothrin (LTC) to induce oxidative stress in the tissues of albino mice. Antioxidants are any substance that delay or inhibits oxidative damage to a target molecule. At a time one antioxidant molecule can react with single free radicals and are capable to neutralize free radicals by donating one of their own electrons, ending the carbon-stealing reaction. Antioxidants prevent cell and tissue damage as they act as scavenger. Cell produce defense against excessive free radicals by their preventative mechanisms, repair mechanisms, physical defenses and antioxidant defenses

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(Jacob, 1995). A variety of components act against free radicals to neutralize them from both endogenous and exogenous in origin (Jacob, 1995). These include: Endogenous enzymatic antioxidants; Non enzymatic, metabolic and nutrient antioxidants; Metal binding proteins like ferritin, lactoferrin, albumin and ceruloplasmin; Phytoconstituents and phytonutrients. The body produces different antioxidants (endogenous antioxidants) to neutralize free radicals and protect the body from different disease leads by the tissue injury. Exogenous antioxidants are externally supply to the body through food also plays important role to protect the body.

The body has developed several endogenous antioxidant defense systems classified into two groups such as enzymatic and non enzymatic. The enzymatic defense system includes different endogenous enzymes like superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR) and non enzymatic defense system included vitamin E, vitamin C and reduced glutathione (GSH) (Jacob, 1995; Harris, 1992). Free radicals are fundamental to any biochemical process and represent an essential part of aerobic life and our metabolism. They are continuously produced by the body via enzymatic and non-enzymatic reactions like chain reaction, the phagocytosis, prostaglandin synthesis, cytochrome P450 system and oxidative phosphorylation (i.e. aerobic respiration) in the mitochondria (Tiwari, 2004; Halliwell, 2007; Pacher *et al.,* 2007). ROS and RNS are the products of normal cellular metabolism, having both deleterious and beneficial effect in the body (Valko *et al.,* 2004).

At low or moderate concentration some of the free radicals plays beneficial physiological role *in vivo* this include defense against infectious agents by phagocytosis, energy production, cell growth, function in different cellular signaling systems and the induction of a mitogenic response at low concentrations (Davies, 1991; Poli *et al.,* 2004). Free radicals occur continuously in all cells as part of normal function. Oxygen free radicals are detrimental to the integrity of biological tissue and mediate their injury. The mechanism of damage involves lipid peroxidation, which destroys cell structures, lipids, proteins and nucleic acids. They cause damage to cell membranes with the release of intracellular components, leading to further tissue damage (Valko *et al.,* 2004; Poli *et al.,* 2004). Antioxidant enzymes and non enzymatic defense system minimizes the harmful effect of ROS by various antioxidant mechanism.

Oxidative stress is a harmful condition that occurs when there is an excess of ROS and/or a decrease in antioxidant levels, this may caused tissue damage by physical, chemical, psychological factors that lead to tissue injury in human and causes different diseases (Tian et al., 2007). Living creatures have evolved a highly complicated defense system and body act against free radical-induced oxidative stress involve by different defense mechanism like preventative mechanisms, repair mechanisms, physical defenses and antioxidant defenses (Valko *et al.,* 2007). Oxygen derived free radical reactions have been implicated in the pathogenesis of many human diseasesincluding (Valko *et al.,* 2007; Pham-Huy *et al.,* 2008; Agarwal and Prabakaran, 2005; Pourmorad, 2006; O'donovan and Fernandes, 2004; Dufor *et al.,* 2007; Gupta *et al.,* 1997; Kehrer and Smith, 1994; Sen *et al.,* 2009): Neurodegenerative disorder like alzheimer's disease, parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, memory loss and depression; Cardiovascular disease like atherosclerosis, ischemic heart disease, cardiac hypertrophy, hypertension, shock and trauma; Pulmonary disorders like inflammatory lung diseases such as asthma and chronic obstructive pulmonary disease; Diseases associated with premature infants, including bronchopulmonary, dysplasia, periventricular leukomalacia, intraventricular hemorrhage, retinopathy of prematurity and necrotizing enterocolitis; Autoimmune disease like rheumatoid arthritis; Renal disorders like glomerulonephritis and tubulointerstitia lnephritis, chronic renal failure, proteinuria, uremia; Gastrointestinal diseases like peptic ulcer, inflammatory bowel disease and colitis; Tumors and cancer like lung cancer, leukemia, breast, ovary, rectum cancers etc.

MATERIAL AND METHODS

Chemical Substance

Lambda cyhalothrin, a synthetic pyrethroid has been considered for this toxicology study. The effective dose 4.8 mg/kg/day given orally in corn oil vehicle for 10, 20 and 30 days. The oral LD_{50} for Lambda cyhalothrin is 24 mg/kg body weight.

Experimental Animal

The present study was carried with on albino mice weighing 30±5g. The animals were housed and were kept under normal environmental conditions of temperature and humidity. Commercial standard diet and water were continuously and regularly supplied ad libitum throughout the experimental period.

Experimental design

Mice were divided equally into four groups (n = 10). Group (1) with normal saline and used as a control. Group 2, 3 & 4 treated orally with LTC at a dose of 1/5 LD_{50} that is 4.8 mg/kg body weight (w.t.), for 10, 20, 30 days. The control and experimental animals after a stipulated period (i.e. on 11^{th}, 21^{st} and 31^{st} day) were sacrificed and the tissues were quickly isolated, cleaned in physiological saline and processed immediately for microscopic analysis under ice-cold conditions. The tissues were also quickly isolated and were kept in deep freezer at -80°C and used for biochemical analysis.

Biochemical studies

Biochemical studies such as Superoxide dismutase activity was measured as the inhibition of photo reduction of nitro blue tetrazolium (NBT) by an enzyme as per the method of Beachamp and Fridovich (1971); Catalase activity was measured by the following method of Aebi, (1984); Se-dependent glutathione peroxidase GPx was measured as the inhibition of photo reductionof nitro blue tetrazolium (NBT) by an enzyme as per the method of Flohe and Gunzler (1984); GR activity was determined by a slightly modified method of Carlberg and Mannervik, (1985).

Statistical analysis

Statistical analysis was carried out using one-way analysis of variance (ANOVA). This was done to compare control and

treated groups, followed by post-hoc analysis (Dunnett's test) using SPSS (Statistical Package for Social Sciences). The data were presented in the form of mean ± Standard Deviation. The difference was considered statistically significant if $p < 0.05$.

RESULTS AND DISCUSSION

In the present study, alterations are observed in all the enzymes related to detoxification mechanism. The activities of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione reductase (GR) were significantly decreased due to Lambda-cyhalothrin exposure. Modern civilization, use of different chemicals, pesticides, pollutant, smoking and alcohol intake and even some of synthetic medicine increases the chance of disease due to free radicals More or less the free radicals plays a role in health of modern era and the diseases caused from free radical are becoming a part of normal life.

Pesticides have become an integral constituent of the ecosystem due to their widespread use, distribution, and the stability of some of the pesticides in the environment. Pesticide exposure may play a major role in increased oxidative stress of the organisms and may result in altered disease susceptibility. Free radicals cause cell injury when they are generated in excess or when the antioxidant defense is impaired. Free radicals and ROS can readily react with most bio-molecules starting a chain reaction of free radical formation. It leads to oxidative stress and disrupt the balance between ROS production and antioxidant homeostasis. In order to stop this chain reaction, a newly formed radical must either react with another free radical, eliminating the unpaired electrons or react with a free radical scavenger or primary antioxidant. Low levels of ROS are vital for many cell signaling events and are essential for proper cell functions. For example superoxide is necessary for proper immune function (Oury *et al.,* 1996). Under normal physiological functions a balance exists between

Table 1. Changes in SOD activity (Superoxide anion reduced/mg of protein/minute) levels in different tissues of albino rat exposed to sub lethal dose of Cartaphydrochloride. Values in parentheses indicate percent change over control

Name of the Tissue	Normal Control	10 days	20 days	30 days	
Intestine					F Value
Mean	1.105±	1.5089	1.378	1.301	9.868
SD	0.09924	±0.1497	±0.1346	±0.1369	P Value
		(36.48)	(24.64)	(17.76)	.000
Testis					F Value
Mean	0.6805	0.9209	0.8225	0.7594	107.333
SD	±0.01819	±0.0356	±0.0241	±0.0109	P Value
		(35.32)	(20.86)	(11.6)	.000

All the values in the table are represented as Mean ± SD.
The means of four groups are compared using one way ANOVA
Post Hoc was done using Dunnet's Multiple Range Test
Values in parenthesis denote percent change over respective saline control.

Table 2. Changes in Catalase activity (μ moles of H_2O_2 decomposed /mg protein/min) levels in different tissues of albino rat exposed to sublethal dose of Cartaphydrochoride. Values in parentheses indicate percent change over control

Name of the Tissue	Normal Control	10 days	20 days	30 days	
Intestine					F Value
Mean	0.3206±	0.4455	0.3813	0.3562	136.83
SD	0.0058	±0.01138	±0.0145	±0.01046	P Value
		(38.95)	(18.93)	(11.1)	.000
Testis					F Value
Mean	0.0442	0.0703	0.0603	0.0544	78.708
SD	±0.00148	±0.00229	±0.00439	±0.00312	P Value
		(59.2)	(36.53)	(23.28)	.000

All the values in the table are represented as Mean ± SD.
The means of four groups are compared using one way ANOVA
Post Hoc was done using Dunnet's Multiple Range Test
Values in parenthesis denote percent change over respective saline control.

Table 3. Changes in GPx activity (Superoxide anion reduced/mg of protein/minute) levels in different tissues of albino rat exposed to sub lethal dose of Cartaphydrochoride. Values in parentheses indicate percent change over control

Name of the Tissue	Normal Control	10 days	20 days	30 days	
Intestine					F Value
Mean	0.5727	0.366	0.4541	0.5127	165.75
SD	±0.0137	±0.0104	±0.0243	±0.0151	P Value
		(36.08)	(20.69)	(10.46)	.000
Testis					F Value
Mean	0.3858	0.2449	0.3014	0.3388	70.473
SD	±0.0115	±0.0268	±0.01186	±0.0144	
		(36.5)	(21.87)	(12.19)	P Value
					.000

All the values in the table are represented as Mean ± SD.
The means of four groups are compared using one way ANOVA
Post Hoc was done using Dunnet's Multiple Range Test
Values in parenthesis denote percent change over respective saline control.

Table 4. Changes in GR activity (µmoles of NADPH oxidized/mg protein/hour) levels in different tissues of albino rat exposed to sub lethal dose of Cartaphydrochoride. Values in parentheses indicate percent change over control

Name of the Tissue	Normal Control	10 days	20 days	30 days	
Intestine					F Value
Mean	0.5725	0.352***	0.4341**	0.5034*	144.70
SD	±0.01363	±0.02139	±0.02869	±0.01968	P Value
		(38.39)	(24.17)	(12.07)	.000
Testis					F Value
Mean	0.3165	0.2013***	0.2249**	0.2797**	79.710
SD	±0.01483	±0.01311	±0.01724	±0.011144	P Value
		(36.37)	(28.92)	(11.6)	.000

All the values in the table are represented as Mean ± SD.
The means of four groups are compared using one way ANOVA
Post Hoc was done using Dunnet's Multiple Range Test
Values in parenthesis denote percent change over respective saline control.

the levels of ROS production during normal cellular metabolism and the level of endogenous antioxidants, which serve to protect tissue from oxidative damage. Disruption of this balance, either through increased production of ROS or decreased levels of antioxidants, produces a condition referred to as Oxidative Stress.Under conditions of normal metabolism, the continual formation of ROS and other free radicals is important for normal physiological functions (i.e. ATP generation, metabolic processes) and cellular redox reactions. However, excessive generation of free radicals can occur due to endogenous biological or exogenous environmental factors, such as chemical exposure, pollution or radiation. Oxidative stress, generated by xenobiotics, induces disturbances in antioxidant enzyme systems (Gabbianelli *et al.,* 2002).

Several workers observed the decreased levels of SOD, CAT, GPx and GR in different animal models and tissues under toxic stress conditions. Bagchi *et al.* demonstrated that pesticides induce the production of ROS and oxidative damage to tissues. de Liz Oliveira Cavalli found that exposure to glyphosate causes oxidative stress and activates multiple stress-response pathways leading to Sertoli cell death in prepubertal rat testis. The role of oxidative stress in immune cell toxicity induced by the pesticides lindane, malathion, and permethrin was examined by Olgun and Misra. Hassoun *et al.* reported that chlordane produces oxidative tissue damage based on the levels of hepatic lipid peroxidation and DNA damage. The joint action of pyrethroids, lambda-cyhalothrin (LC) in combination with organophosphates, fenitrothione (FNT) on antioxidant defense system and lipid peroxidation biomarkers in rat testes was studied. The results suggest that incubation of testes homogenate with different concentrations of insecticide mixture for different time intervals significantly decreased the activity of antioxidant enzymes, like glutathione S-transferase (GST), superoxide dismutase (SOD) and catalase (CAT), and the level of reduced glutathione (GSH) El-Demerdash FM (2013).

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