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Short Communication

How Deltamethrin Produces Oxidative Stress in Liver and Kidney

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Abstract

Deltamethrin (DEL) is a synthetic pyrethroid widely used as an insecticide. The aim of our study was to determine the effect of a single exposure of female albino Swiss mice to DEL (at doses of 8.3 mg/kg, 20.75 mg/kg, or 41.5 mg/kg) on parameters of liver and kidney function and activities of antioxidant enzymes in these organs. The activity of alanine transaminase (ALT) in the blood sera of the experimental animals was not significantly elevated after exposure to DEL. Asparagine transaminase (AST) activity was significantly higher in the groups exposed to the moderate and the highest dose of DEL. The levels of creatinine in the blood sera of the experimental animals did not significantly differ among the groups. The activities of superoxide dismuthase (SOD) and glutathione peroxidase (GPx) were significantly reduced in the livers of mice exposed to the highest dose of DEL in comparison with controls. In the kidneys, however, the SOD and GPx activities were significantly elevated after exposure to the highest dose of DEL. In conclusion, DEL produces oxidative stress in the livers and, to a lesser degree, the kidneys of exposed animals.

Keywords: deltamethrin, antioxidant enzymes, oxidative stress

Introduction

Deltamethrin (DEL) is a synthetic pyrethroid. Pyrethroids are used as an insecticides [1], acaricides, and repellents [2]. They are used for public health improvement in malaria prevention actions [3]. Global climate change, with temperature increasing by 2 to 3ºC, makes the population living in endemic zones of malaria increase by 3 to 5% [4]. It also increases the risk of growing populations of insect pests destroying crops. Due to their environmental risk, organochlorine pesticides were withdrawn from the market (i.e., DDT in Poland in 1973). However, their traces are still present in arable soils in our country [5]. Another problem is obsolete pesticides posing a great environmental hazard [6]. Therefore, the use of pyrethroids, which are less persistent in the environment, is expected to increase. Now up to 30% of all insecticides used in agriculture are pyrethroids. Poland has 13 registered pyrethroids. One of them is DEL. The current annual use of pyrethroids in Poland is estimated to be more than 80,000 kg used as an active ingredient [7].

Pyrethroids are neurotoxins acting on voltage-gated sodium channels in neuron cell membranes [8, 9]. Intoxication produces paralysis and death of target organisms [10]. For over half a century it was believed that pyrethroids acted only via fast disregulation of the nervous system, without any significant cytotoxic effect. However, there is evidence that exposure to pyrethroids may produce neuron death in adult animals [11, 12], inhibition of nervous system development in rodent newborns [13-15], and damage to internal organs via toxic metabolites [16-18]. Recent studies show that pyrethroids

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impair kidney functioning [19], cause hepatic toxicity, change blood morphology, disrupt the endocrine system [20-22,], and lead to oxidative stress (OS) [24, 25].

Oxidative stress is an imbalance between reactive oxygen species (ROS) and antioxidants. The ROS can damage DNA, proteins, and lipids, and change a cell's metabolism, and affect gene expression and post-translational modifications of proteins, which accelerates ageing, neurodegeneration, and development of atherosclerosis, hypertension, type II diabetes, and cancer [26, 27]. Superoxide dismuthase (SOD) and glutathione peroxidase (GPx) are antioxidant enzymes ubiquitous in living organisms acting as an endogenous defense against ROS [28, 29].

Chemically, pyrethroids are esters of alcohols and vinyl cyclopropane carboxylic acids. DEL is ((S)-alpha-cyano-3-phenoxybenzyl-91R,cis)-2,2-dimethyl-3-(2,2-dibromovinyl)-cycloprpanecarboxylate. It is the most potent neurotoxic compound of the PYR group [30, 31]. It is used in the form of (cis)isomer [32]. DEL is rapidly absorbed after oral or intraperitoneal administration and quickly reaches its main target: voltage sensitive sodium channels in the central nervous system [33, 34]. DEL is detoxified in mammals by hydrolysis of the ester bond by liver and plasma carboxyesterases to relatively non-toxic acidic and alcoholic moieties [8]. Cytochrome P450s in liver microsomes can catalyze aromatic hydroxylation of DEL [35]. These processes are followed by sulfate and glucuronide conjugation. Products of DEL metabolism are passed with urine. The metabolites of DEL most often detected in urine samples in human biomonitoring studies are cis-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (Br_2CA), and 3-phenoxybenzoic acid (3-PBA) [36]. 3-PBA and Br_2CA are detected in higher concentrations in urine samples from humans living in rural areas [37], but seem to be ubiquitous in men and women of all ages without job-related exposure to pesticides, suggesting wide exposure of the general population to DEL [36]. The current investigation aimed to explore the effect of single exposure to mice to DEL on parameters of liver and kidney function and activities of antioxidant enzymes in these organs.

Materials and Methods

All the experimental procedures were conducted with respect for the law regulations of the European Community and Poland. They were conducted at the Department of Hygiene, Medical University of Lublin, Poland. The Local Ethics Committee for Animal Experiments in Lublin approved the experiment (Opinion No. 4/2009, dated: 9 January 2009).

Non-gravid female albino Swiss mice weighing 18-24 g of approximately six weeks of age purchased from a licensed breeder (T. Górzkowski, Warsaw, Poland) were used in the study. All animals were given a seven-day acclimation period and maintained on a 12 hr light/dark cycle. Food and tap water were provided *ad libitum.* Temperature was maintained at 21±2ºC. The mice were randomly divided into four groups of eight animals each.

Deltamethrin was purchased from the manufacturer (Institute of Industrial Organic Chemistry, Annopol, Warsaw, Poland). As pyrethroids poorly dissolve in water, Tween 60 (poloxyethylene sorbitan monostearate) purchased from Laboratorium Reagenzien, Germany was used to prepare solutions in bi-distilled water.

On the first day of the experiment mice from each group were once injected intraperoitoneally:

- Group I (control) received saline (10 ml of saline per 1,000 g of mice body mass; a mouse of body mass 20 g received 0.2 ml saline *ip* per injection).
- Group II received DEL at a dose of 8.3 mg/kg of body mass (10 ml of solution was prepared per 1,000 g of mice body mass; 0.1 ml of Tween was used pr 10 ml of solution; a mouse of body mass 20 g received 0.2 ml solution *ip* per injection).
- Group III received DEL at a dose of 20.75 mg/kg of body mass.
- Group IV received DEL at a dose of 41.5 mg/kg of body mass.

On the second day mice were decapitated, and their blood samples were collected to clot in order to measure ALT and AST activity in the blood sera and creatinine concentration. Livers and kidneys were used to measure

Table 1. Effect of DEL on ALT, AST, and creatinine in the blood sera, SOD, and GPx activities in the livers and kidneys of experimental animals; N = 8, *p < 0.05 vs. control.

	Control	DEL 8.3 mg/kg	DEL 20.75 mg/kg	DEL 41.5 mg/kg
ALT (U/l)	38±3	40±4.7	39.3±1.2	43±8.5
AST (U/l)	170±5.8	235±16.6	307±13.6*	386.7±113.5*
SOD activity in livers (U/g of tissue)	2,912.3±171	2,337.3±187	2,150±261*	2,126±156*
GPx activity in livers (U/g of tissue)	34.4±13.3	37.5±6.2	22±4.4	11±2.2*
Creatinine (mg%)	0.25±0.1	0.2±0.1	0.2±0.1	0.3±0.1
SOD activity in kidneys (U/g of tissue)	910±55.7	868±151.4	918±227.5	1,556±152*
GPx activity in kidneys (U/g of tissue)	5.3±0.7	26.7±3*	27.6±6.8*	30.3±3.5*

SOD and GPx activities. The SOD activity was measured with the use of a RANSOD kit manufactured by Randox Laboratories Ltd., with a spectrophotometric method [38]. The livers were homogenized with an MPW-120 mechanical blender in a 0.1M buffer of Tris-HCl, 7.4 pH (0.5 g of tissue per 5 ml buffer). The homogenates were centrifuged for 15 min twice at 5,000 rpm. The supernatants were collected for SOD activity measurement.

The activity of GPx was measured with the use of a RANSEL kit manufactured by Randox Laboratories Ltd. Using the spectrophotometric method [39].

The results obtained were shown as means ±SEM, and evaluated by one-way analysis of variance ANOVA followed by Dunnett's test. The p value < 0.05 was considered statistically significant.

Results

The activity of ALT in the blood sera of the experimental animals was not significantly elevated after exposure to DEL (Table 1). The AST activity was significantly higher in the groups exposed to the moderate and the highest dose of DEL. The levels of creatinine in the blood sera did not significantly differ among the groups. The activities of SOD and GPx were significantly reduced in the livers of mice exposed to the highest dose of DEL in comparison with controls. In the kidneys, however, the SOD and GPx activities were significantly elevated after exposure to DEL.

Discussion and Conclusion

Pyrethroids are potent neurotoxins, as confirmed in our former studies [40, 41]. In one of our previous experiments we found that DEL administered to mice at the dose of 16.6 mg/kg for 14 subsequent days increased urea concentrations, but did not affect the level of creatinine [19]. This time we aimed to find out if higher doses of DEL could impair liver and/or kidney function and produce oxidative stress in these organs.

Healthy organisms are able to combat oxidative stress with enzymatic (SOD and GPx) and non-enzymatic antioxidant systems. However, after exposure to sublethal doses of pesticides, which is an extreme oxidative challenge, the antioxidant system may become overwhelmed and fail [42].

The depletion of the antioxidant enzymes found in the livers in our study show that oxidative stress occurs in the liver after exposure to the highest dose of DEL. Our study showed a significant decrease in GPx and SOD activities in the livers of experimental animals exposed to the highest dose of DEL. However, ALT activities were not significantly elevated. The AST activities were significantly elevated in mice exposed to the moderate and highest doses of DEL. It is worth adding that AST is less specific for hepatic lesion, and it may be elevated in results of muscle or brain damage, too. This indicates that DEL produces multi-organ damage. Dubey et al. reported significant hepatic oxidative stress and hepatic damage in rats exposed to DEL administered with fluoride [25]. The results of the experiment carried out by Galal et al. seem to confirm the theory that DEL produces oxidative stress, as they showed that exposure to DEL caused a significant increase in lipid peroxidation, nitric oxide concentration, and DNA fragmentation percentage, plus a significant reduction of total antioxidant capacity of DEL-treated groups of rats [43]. Other authors have demonstrated that pyrethroids produce oxidative stress in exposed cells, which leads to a reduction in concentration of thiol groups [44].

According to Popa-Wagner [45], in oxidative stress an up-regulation of genes coding antioxidant enzymes occurs. Glutathione peroxidases are enzymes containing selenium (Se). The activity of GPx in the cells may increase until an adequate supply of Se in the diet maximizes the enzyme activity [46]. Apparently, the metabolites od DEL (3-PBA and Br_2CA) do not pose a great risk to kidney functioning as creatinine concentrations in the blood sera were not elevated. The SOD and GPx activities in the kidneys were elevated, suggesting that the kidneys were able to neutralize the ROS species formed in response to intoxication with DEL.

In conclusion, DEL produces oxidative stress in the livers and, to a lesser degree, in the kidneys of exposed animals.

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