Pharmacological Reports 67 (2015) 535–541

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Original research article

Subacute poisoning of mice with deltamethrin produces memory impairment, reduced locomotor activity, liver damage and changes in blood morphology in the mechanism of oxidative stress

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ARTICLE INFO

Article history:
Received 23 October 2014
Received in revised form 16 December 2014
Accepted 17 December 2014
Available online 31 December 2014

Keywords:
Pyrethroid
Deltamethrin
Locomotor activity
Memory
Oxidative stress

ABSTRACT

Background: Deltamethrin (DEL) is a synthetic pyrethroid (PYR) insecticide, potent neurotoxicant. The current investigation was envisaged to explore behavioral, biochemical and morphologic effects of subacute poisoning with DEL in mice and to find one common mechanism of these changes.
Methods: Mice were daily injected *ip* with different doses of DEL: 8.3, 20.75 or 41.5 mg/kg bw for 28 days. Their memory retention in passive avoidance task (PA), fresh spatial memory in a Y-maze and locomotor activity were measured once weekly. On day 29, blood morphology, alanine transaminase (ALT) activity and creatinine concentration in the blood sera, superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities were measured in the livers and kidneys. Livers were examined with light microscopy.
Results: Significant impairment of memory retention was recorded on day 2, 7 and 28 after exposure to DEL. Fresh spatial memory was significantly impaired by the highest dose of DEL on day 1, 14 and 28. Locomotor activity was reduced at every stage of experiment in all the groups exposed to DEL. In the animals exposed to the highest dose of DEL activities of alanine transaminase (ALT) and SOD were elevated, GPx was reduced, lymphocyte infiltrates were detected in the livers and there were changes in blood morphology.
Conclusion: The results obtained indicate that liver and bone marrow, apart from the central nervous system (CNS) are damaged in the course of subacute poisoning with DEL. The possible common mechanism of the damage is oxidative stress.
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Introduction

Deltamethrin (DEL) is a synthetic type II pyrethroid (PYR) of insecticidal properties commonly used in agriculture to increase crops. Since PYRs replace organophosphorus (OP) insecticides, they become chemicals of choice in many agriculture-based countries. PYR insecticides have high insecticidal potency and are not persistent in the environment [1], therefore their use is increasing. In European countries like Poland the use of PYRs has doubled in the years 2005–2010 to be over 87,000 kg in relation to active substances [2]. There are 13 PYRs registered in Poland and one of them is DEL. Concurrently, there is a growing number of recent reports on DEL's toxicity to humans, pets and experimental animals [3–6]. Therefore a question arises whether repeated exposure of non-target organisms to DEL leads to any chronic disturbance in behavior and metabolism.

Mammals are non-target organisms for DEL. Humans may be exposed to the highest doses of PYRs during application in agriculture [7], but members of the general population are chronically nonoccupationally exposed to low doses mainly *via* food of plant origin [8].

PYRs are neurotoxins acting primarily on the voltage-sensitive sodium channels in excitable cells (neurons and muscles). The altered sodium channels cause repetitive firing and depolarizing block in neurons [1]. In target organisms acute poisoning with PYRs results in motor activity impairment. In insects moderate doses of PYRs produce hyperexcitability, an increase in motor activity with altered mode of flying or walking [9]. Higher doses cause immobility of walking insects and falling down among flying insects. The highest doses cause immediate hindlimb paralysis, movement incoordination and eventually prostration and death.

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http://dx.doi.org/10.1016/j.pharep.2014.12.012
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On one hand PYRs are considered to be relatively safe for mammals because of constant and higher than in insects internal body temperature, faster metabolism and lower sensitivity of sodium channels [1]. On the other hand however, over 30 years ago when PYRs were divided into types I and II, the classification was based on their structure and clinical signs of acute intoxication described in mammals and nobody expected at that point that exposure of humans to PYRs may become chronic. Type I compounds do not contain a cyano group, while type II (where DEL belongs) do. The major clinical sign of acute rodent poisoning with type I PYRs is tremor (T-syndrome), whereas choreoathetosis and salivation (CS-syndrome) show up in acute poisoning with type II PYRs [10,11]. As shown above acute PYR toxicity was extensively investigated, however sparse data about effects of subacute or chronic poisoning in mammals are available. Since the 1980' a growing body of evidence was collected indicating multiple modes of PYR's action: inhibition of mitotic index, chromosomal aberrations [12], neuron death in adult animals [13], inhibition of nervous system development in rodent newborns [3] and damage to internal organs *via* toxic metabolites [14]. In recent studies PYRs were shown to act as endocrine disruptors [15,16], produce reproductive toxicity in mice [17], and oxidative stress [18]. Oxidative stress is an imbalance between reactive oxygen species (ROS) and antioxidants. The ROS can damage DNA, proteins and lipids, change cell's metabolism, affect gene expression and posttranslational modifications of proteins, which accelerates aging, neurodegeneration and development of atherosclerosis, hypertension, type II diabetes as well as cancer [19–21]. SOD and GPx are antioxidant enzymes ubiquitous in living organisms acting as an endogenous defense against ROS [22,23].

Chemically PYRs 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)-cyclopropanecarboxylate. It is the most potent neurotoxic compound of PYR group [24,25]. It is used in the form of (cis) isomer [26]. DEL is rapidly absorbed after oral or intraperitoneal administration and quickly reaches its' main target: voltage sensitive sodium channels in the central nervous system [27,28]. DEL is detoxified in mammals by hydrolysis of the ester bond by liver and plasma carboxyesterases to relatively non-toxic acidic and alcoholic moieties [1]. Cytochrome P450s in liver microsomes can catalyze aromatic hydroxylation of DEL [29]. 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) [30]. 3-PBA and Br_2CA are detected in higher concentrations in urine samples from humans living in rural areas [31], 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 [30]. The current investigation aimed to explore behavioral and biochemical effects of subacute poisoning with DEL in animal model and to find one common mechanism of these changes.

Materials and methods

Subjects

The experiments were carried out on adult non-gravid female albino Swiss mice purchased from a licensed breeder (T. Górzkowski, Warsaw, Poland). All animals were given a 7-day acclimation period. The animals were weighing 18–24 g at the beginning of the study. They were housed in colony cages. The laboratory temperature was 21 ± 2 °C on a 12:12 light/dark cycle. The animals had free access to food and tap water *ad libitum*. The experimental groups were made up at random. A total of 96 animals were used in the experiment. The experiments were performed between 8:00 a.m. and 6:00 p.m. The experimental protocols and procedures described in this paper were approved by the Local Ethics Committee for Animal Experiments in Lublin (Opinion No. 4/2009, dated: January 9th 2009) and complied with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Body mass of the experimental animals was recorded daily before DEL injection.

Animals were divides into 12 groups of 8 animals each:

Groups 1–3: control receiving saline *ip* daily (10 ml of saline per 1000 g of mice body mass. A mouse of body mass 22 g received 0.22 ml saline in one injection).

Groups 4–6: receiving DEL at the dose of 8.3 mg/kg bw (8.3 mg of DEL was dissolved in 9.9 ml of saline with 0.1 ml of Tween as pure PYRs poorly dissolve in water. 10 ml of solution was prepared per 1000 g of mice body mass. A mouse of body mass 22 g received 0.22 ml solution *ip* in one injection).

Groups 7–9: receiving DEL at the dose of 20.75 mg/kg bw (20.75 mg of DEL was dissolved in 9.9 ml of saline with 0.1 ml of Tween).

Groups 10–12: receiving DEL at the dose of 41.5 mg/kg bw (41.5 mg of DEL was dissolved in 9.9 ml of saline with 0.1 ml of Tween). Injections were repeated once daily for 28 days.

Chemicals

Deltamethrin ((S)-alpha-cyano-3-phenoxybenzyl-91R,cis)-2,2-dimethyl-3-(2,2-dibromovinyl)-cyclopropanecarboxylate 99% purity was purchased from the manufacturer (Institute of Industrial Organic Chemistry, Annopol, Warsaw, Poland).

Tween 60 (polyoxyethylene sorbitan monostearate) was purchased from Laboratorium Reagenzien, Germany.

Behavioral tests

Passive avoidance task

Animals from groups 1, 4, 7, 10 were tested in passive avoidance task. The step-through passive avoidance task (PA) relies on the natural preference of rodents for dark, enclosed spaces. PA is regarded as a good measure of long-term memory retention [32]. Thirty minutes after DEL injection each animal was placed in a well lit box (15 cm × 12 cm × 15 cm) adjacent to a darkened one. The dark box had an electric grid floor. Thirty seconds after placing an animal in the center of the illuminated box, a passage joining the two boxes was opened. After entering the dark box, the mouse was affected with an electric foot shock (2 mA for 2 s). Twenty four hours after the training memory retention test was conducted. The latency to enter the darkened box was recorded. The test ended when the mouse entered the darkened box or when 180 s elapsed. Training was repeated on day 1, 6, 13 and 27. PA test was done on day 2, 7, 14 and 28.

Y-maze

Animals from groups 2, 5, 8, 11 were tested in a Y-maze on day 1, 7, 14, 28. The Y-maze is considered as a measure of spatial working memory [33]. Thirty minutes after DEL injection the mice were individually placed in the Y-maze consisting of 3 compartments measuring 10 cm × 10 cm × 10 cm at the angle of 120°. The Y-maze had no floor. Every time it was placed on a clean sheet of paper on a table top in order to prevent odor clues. Alternation (defined as consecutive entries into all three sections without repetitions) was scored. The percent alternation was calculated as the ratio of actual possible alternations (defined as the total number of section entries − 2) × 100. The ability to alternate

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