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EFFECT OF DELTAMETHRIN ON DRUG METABOLIZING ENZYMES IN MALE MICE LIVER

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ABSTRACT

The present study was undertaken to investigate the effects of a single (24 h) and repeated (7 days) doses of deltamethrin (10 mg/kg body weight daily) on hepatic drug metabolizing enzymes. The hepatic content of microsomal protein, cytochrome P450 and b_5, activities of NADPH cytochrome C reductase, amidopyrine N-demethylase, aniline-4-hydroxylase, glutathion S-transeferase and the level of thiobarbituric acid reactive substances (TBARS) were determined. The obtained results indicated that a single dose of deltamethrin had no significant effect on hepatic microsomal proteins, cytochrome b_5, amidopyrine N-demethylase, aniline-4-hydroxylase, or TBARS. However, it significantly decreased ($p<0.05$) the activity of cytochrome P450, and increased the activities of NADPH cytochrome C reductase ($p<0.001$) and glutathion S-transeferase ($p<0.05$). Repeated doses of deltamethrin significantly decreased the activities of hepatic microsomal proteins ($p<0.05$) and amidopyrine N-demethylase ($p<0.001$), and increased the activities ($P<0.01$) of other studied enzymes. The obtained results indicated that single and repeated doses of deltamethrin had marked effects on hepatic drug metabolizing enzymes.

Keywords: Delamethrin,, mice, hepatic microsomal enzymes, TBARS.

INTRODUCTION

Deltamethrin is a synthetic pyrethroid with potent insecticidal property. The technical grade of deltamethrin is composed of eight stereomeric esters (four cis and four trans isomers) of the dibromo analogue of chrysanthemic acid, 2,2-dimethyl-3-cyclopropancarboxylic acid (Manna *et al.* , 2005 and Dayal *et al.* , 2003). Deltamethrin is extensively used as an octoparasiticide in animals and as an insecticide in crop production and public health program (WHO, 1990). Some of the toxic actions of deltamethrin are based on tissue residue level and effects after repeated daily oral administration on cytochrome P450, cytochrome b_5 and antioxidant status; pyrethroids have been shown to interact with the hepatic xenobiotic metabolizing enzymes (Anadon *et al.* , 1996). Covalent binding of deltamethrin with hepatic microsomal proteins has suggested the involvement of cytochrome P450 monooxygenases in the metabolism of deltamethrin (Catinot *et al.* , 1989).

Cytochrome P450-dependent monooxygenases are very important enzymatic systems involved in the metabolism of a phenomenal number of endogenous and exogenous compounds (Hodgson, 1985). P450 monooxygenases have been found in all living systems examined. The overall reaction of P450 monooxygenases-mediated metabolism can be expressed as follows:

$$\mathbf{RH+O_2+NADPH+H^+ \rightarrow ROH+H_2O+NADP^+}$$ **(Where RH is the substrate)**

The majority of cytochrome P450s on eukaryotes are located in the endoplasmic reticulum and require the flavoprotein NADPH cytochrome P450 reductase for reducing equivalents. In addition to cytochrome P450 and

cytochrome –C- reductase, cytochrome b_5 is sometimes needed, depending upon the substrate and/or the P450 isoform involved. Cytochrome b_5 may be important in donating the second electron from the reduced form of nicotinamide di-nuclutide (NADH) to P450 or by allosterically regulating substrate binding to P450 (Epstein *et al.* , 1989 and Zhang and Scott, 1996).

The present study was undertaken to determine the effect of single and repeated oral doses for 7 days of deltamethrin on mixed function of oxidase systems.

MATERIAL AND METHODS

Chemicals. Deltamethrin (purity= 98%) was purchased from Agromen Chemicals Co. ltd. China. Reduced glutathione (GSH), 1-chloro-2,4-dinitrobenzene, nicotinamide adenosine dinucleotide phosphate (NADPH), amidopyrine, cytochrome C, thiobarbituric acid and all other chemicals were purchased from Sigma Chemical Company (Saint Louis, USA). Use of deltamethrin was approved by the Animal Care Committee and met all guidelines for its use.

Animals. Twenty four male mice with average body weight of 25-30 g were obtained from Medical Research Institute, Alexandria University, Egypt, and acclimated for two weeks prior to the experiment. They were assigned to three groups and housed in Universal galvanized wire cages at room temperature (22-25 °C) and in a photoperiod of 12 h/day. Animals were provided with a commercial balanced diet.

Experimental design. The three groups of mice were randomly assigned for the following: Group I (GI, 12 animals) served as a control and orally treated with saline; group II (GII, 6 animals) was treated orally with a single dose of deltamethrin (10 mg/kg body weight) (Dayal *et al.* , 2003) and group III (GIII, 6 animals) was treated orally with deltamethrin (10 mg/kg body weight/day) for seven days. Six animals of the control group (GI.1), and all GII animals were decapitated 24 h after deltamethrin treatment; the rest of the control group (GI.2), and GIII were decapitated at the end of seven days treatment.

Tissue preparation and assays

Preparation of liver microsomes.

At the end of the treatment, mice were fasted 24 h prior to being sacrificed by cervical dislocation. The abdominal cavity was opened immediately and liver was removed, washed with cold 0.1 M phosphate buffer, pH 7.4, weighed and chilled on ice. All the following procedures were carried out in cold conditions. A 33% (W/V) crude homogenate was prepared in 0.1 M phosphate buffer, pH 7.4 by homogenization with a teflon pestle, using 5 strokes. The crude homogenate was then centrifuged at 11,000 xg for 20 min at 4°C to remove the intact cells, nuclei and mitochondria. The supernatant solution was subsequently centrifuged at 105,000 xg for 60 min at 4°C to sediment the microsomal pellet. The pellet was resuspended in 0.1 M phosphate buffer, pH 7.4, kept in ice bath and used as the enzyme source.

Protein determination.

The protein concentration of the hepatic microsomal fraction was determined by the method of Lowery *et al.* (1951).

Enzyme assays.

Liver microsomal cytochrome P450 and b_5 were determined according to Omura and Sato (1964), using molar extinction coefficient 91 cm^{-1} mM^{-1} for P450 and 185 cm^{-1} mM^{-1} for reduced cytochrome b_5. The activity of microsomal NADPH- cytochrome-C reductase was assayed according to the method of Williams and Kamin (1962). The rate of reduction of cytochrome C was measured at zero and 30 seconds after addition of NADPH at wavelength 550 □m. The activity of this enzyme was calculated by using extinction coefficient of 21 cm^{-1} mM^{-1}

Glutathione-S-transferase activity was assayed according to the method of Habig *et al.* (1974). The incubation mixture contained 30 □g protein of the supernatant fraction, 0.5 ml of reduced glutathione (0.5 mM), 0.1M sodium phosphate buffer, pH 7.3. After preincubation at 37 °C for 5 min the reaction was initiated by adding 50 □L of 1-chloro-2,4-dinitrobenzene (CDNB; 0.5 mM) and incubated at 37°C for another 5 min; the reaction was terminated by the addition of 0.2 ml of trichloroacetic acid solution (33% W/V). After centrifugation, the CDNB conjugate was measured spectrophotometrically at 340 □m. Calculations were made using a molar extinction coefficient of 9.6 cm^{-1} mM^{-1}.

The activity of amidopyrine N-demethylase was measured according to Nash (1953). The incubation mixture (1.71 ml) contained 0.4 ml of 0.1 M Tris-HCl buffer pH 7.4, 0.4 ml of 2.5 □M magnesium chloride, 0.2 ml of 1 mM NADPH, 0.1 ml of microsomal suspension and 0.11 ml of 80 mM amidopyrine. After incubation at 37 °C for 20 min, the reaction was stopped by adding 0.25 ml of 25% zinc sulphate and 0.25 ml of aqueous solution of barium hydroxide. After centrifugation (3,000 rpm for 10 min) the formaldehyde was determined spectrophotometrically from changes in the color intensity of the supernatant at 412 □m.

The activity of aniline 4-hydroxylase was measured according to Kato and Gillette (1965). The incubation mixture (1.71 ml) contained 0.4 ml of 0.08 M Tris-HCl buffer, pH 7.4, 0.4 ml of 0.16 M magnesium chloride, 0.2 ml of 0.03 M NADPH, 0.1 ml of microsomal suspension and 0.11 ml of 0.03 M aniline. After incubation at 37 °C for 20 min, the reaction was stopped by adding 0.5 ml of 15% trichloroacetic acid. After centrifugation (at 3,000 rpm for 10 min), 1 ml of supernatant was added to 0.5 ml of 10% sodium carbonate and 1.5 ml of 2% phenol. After incubation at 37 °C for 30 min, the color developed was measured spectrophotometrically at 630 □m.

Thiobarbituric acid reactive substances (TBARS) were measured in liver microsomes as described by Tapel and Zalkin (1959). The color intensity of the TBARS reactants was measured at 532 □m and a molar extinction coefficient of 156,000 cm^{-1} M^{-1} was used for calculation of the concentration.

Statistical analyses.

Statistical analyses were made to obtain the standard deviation and standard errors of mean. The data for the treated animals were compared with data for the control animals by using the Student's t-test. The level of significance for all experiments was set at $p<0.05$.

RESULTS AND DISCUSSION

The present study is concerned with certain classes of hepatic microsomal enzymes including amidopyrine N-demethylase, NADPH-cytochrome C-reductase, glutathione S-transeferase, aniline 4-hydroxylase, the levels of thiobarbituric acid reactive substances as well as the hepatic content of cytochrome P450 and cytochrome b_5.

Results in Table 1 indicate that the microsomal protein content in the liver of male mice was insignificantly decreased after treatment with deltamethrin (10 mg/kg body weight) as a single dose. On the other hand, repeated dose treatment for 7 consecutive days with deltamethrin significantly ($p<0.05$) decreased hepatic content of microsomal protein by 33%. The hepatic content of P450 was markedly decreased ($p<0.05$) after treatment with deltamethrin for 24 h as a single dose (by 33%), while this content was significantly ($p<0.01$) increased after 7days treatment as a repeated dose. Also, the hepatic content of cytochrome b_5 was insignificantly affected by single dose treatment (24 h), while such content was significantly ($p<0.01$) increased after repeated dose treatment of deltamethrin.

Table 1: Changes of the activity of some drug-metabolizing enzymes (phase I and II) in mice liver treated with deltamethrin after single (24 h) and repeated doses (7 consecutive days) compared with those found for normal mice liver (means ± SE).

Enzymes	Control (GI.1)	Single Dose Treatment 24 h (GII)		Control (GI.2)	Repeated doses 7 Days (GIII)	
Hepatic microsomal proteins	12.30 ± 1.66	11.58 ± 1.24	NS	12.06 ± 1.72	8.07 ±0.65	p< 0.05
Cytochrome P-450	1.22 ± 0.13	0.82 ± 0.11	p<0.05	1.22 ± 0.14	2.55 ±0.37	p<0.01
Cytochrome b_5	0.54 ± 0.04	0.42 ± 0.05	NS	0.56 ± 0.04	1.19 ±0.21	p<0.01
NADPH Cytochrome C reductase	34.15 ± 1.84	52.59 ± 2.67	p<0.001	33.98 ± 1.77	61.89±3.38	p<0.001
Glutathion S-transeferase	0.67 ± 0.07	1.27 ± 0.26	p<0.05	0.68 ± 0.06	4.14 ±0.40	p<0.001
Amidopyrine N-demethylase	37.00 ± 2.17	37.44 ± 2.08	NS	36.45 ± 2.06	18.65±1.42	p<0.001
Anilin-4-hydroxylase	0.19 ± 0.04	0.13 ± 0.01	NS	0.22 ± 0.04	0.86 ±0.08	p<0.001
TBARS	2.47 ± 0.26	2.61 ± 0.47	NS	2.44 ± 0.30	13.24±1.16	p<0.001

Hepatic microsomal protein content was expressed as mg protein/ g liver, cytochrome P450 and Cytochrome b_5 contents were expressed as p mol Cyt./mg microsomal protein, NADPH cytochrome C reductase activity was expressed as p mol cytochrome C reductase/ mg protein/ min, Glutathion S-transeferase activity was expressed as units/mg protein, amidopyrine N-demethylase in liver microsomes was expressed as p mol/ min x kg liver sample, anilin-4-hydroxylase activity was expressed as p mol/ min/ mg protein and thiobarbituric acid reactive substances (TBARS) were expressed as p mol TBARS/g tissue,.

Also number of pesticides cause changes in hepatic microsomal enzymes activity. Some authors showed that synthetic pyrethroids did not markedly influence the microsomal liver enzymes (Riviere *et al.* , 1983 and Habazin-Novak *et al.* , 1985); and others found an increase (Kagan *et al.* , 1986 and Anadon *et al.* , 1988) or decrease (Tang *et al.* , 1987) of their activity. These disparities may result from different methods of pyrethroids administration, different species in the experiments, as well as different parameters determined (Krechniak and Wrzesniowska, 1991).

Riviere *et al.* (1983) found that permethrin, cypermethrin, deltamethrin and fenvalerate cause no or only a moderate increase in hepatic microsomal cytochrome P450 level and NADPH cytochrome P450 reductase activities in the Japanese quail, while a significant increase in hepatic microsomal cytochrome P450 in rats after 5 or 10 daily 10 mg/kg doses of deltamethrin was ascertained by Habazin-Novak and Plestina (1984). Febacher *et al.* (1980) found that permethrin given for 3 days in 100 mg/kg oral doses didn't induce mixed function oxidase activity in male mice, whereas the results of plasma antipyrine kinetics obtained by Anadon *et al.* (1988) indicated that permithrin administered for 3 days in 90 and 180 mg/kg doses was capable for producing a dose-dependant enzyme inducing effect.

The effect of deltamethrin on the hepatic activity of NADPH-cytochrome C-reductase was investigated. The NADPH- cytochrome C-reductase was significantly ($p<0.001$) increased after single and repeated doses of deltamethrin by 54 and 82%, respectively (Table 1).

It has been postulated that the rate-limiting step in the oxidation of some xenobiotics may be due to the rate of reduction of cytochrome P450-substrate complex which is dependent on the activation of NADPH-cytochrome C-reductase and of cytochrome P450 content (El-Mouelhi, *et al.* , 1987), therefore, these essential components of the hepatic microsomal drug metabolizing system were measured. The decrease of cytochrome P450 content might be attributable to the decrease in the level of heme, which is an essential component of cytochrome P450 enzyme since most organic and inorganic compounds were found to inhibit the heme biosynthesis and/or induce heme oxygenase responsible for the degradation of heme (Rocha-e-Silva *et al.* , 2004). Associated with the increase in heme oxygenase activity is a depression in hepatic microsomal cytochrome P450 content and a concomitant decrease in mixed-function oxidase activity (Mains and Kappas, 1977). Moreover, reduction in the level of mixed-function oxidase might also be due to inhibition of both mRNA and protein levels of cytochrome P450 (Degawa *et al.* , 1994). Induction of cytochrome P450 after a 7-day treatment with deltamethrin may be due to the enhancement of metallothionein levels after relatively short time of treatment (Piotrowski and Syzmansak, 1976). Cytochrome b_5 plays a great role in the reduction of cytochrome P450 substerate complex by providing electrons through the NADH pathway. Therefore, the increase in the hepatic content of cytochrome b_5 may increase the rate of biotransformation of drug and carcinogens.

The effect of deltamethrin on the hepatic activity of NADPH-cytochrome C-reductase was investigated. NADPH- cytochrome C-reductase activity is a component of the microsomal mixed-function oxidase system

which catalyses hydroxylation reaction, and this process is of a prime importance in the metabolism of lipids, drugs and other foreign compounds (Vermilion *et al.* , 1981). A wide variety of compounds have the ability to increase or inhibit the drug metabolism by their effect on the activity of NADPH- cytochrome C-reductase. The rate-limiting step in the activation and detoxification of toxic compounds is dependent on the rate of reduction of cytochrome P-450-substerate complex, which in turn is dependent on the activation and turnover rates of NADPH- cytochrome C-reductase, cytochrome b_5 and on the total cytochrome P-450 content (Delvi, 1992). The induction of NADPH- cytochrome C-reductase in the present study could be one of the of the defense mechanisms of the experimental animals to increase the rate of reduction of cytochrome P-450 substrate complex (Sheweita *et al.* , 2001).

The activity of amidopyrine N-demethylase was also studied. The present results indicate that single dose of deltamethrin has no effect on amidopyrine N-demethylase, while the activity was significantly ($p<0.001$) decreased by 49% after repeated dose treatment. Also, the activity of aniline 4-hydroxylase was not affected by a single dose treatment, while repeated doses significantly increased ($p<0.001$) the hydroxylase activity (Table 1).

The activity of amidopyrine N-demethylase was also studied where it decreased at 7 days treatment. The mechanism of inhibition of N-demethylase activity is not known but there are several possibilities (Sheweita *et al.* , 2004). It might be due to the stress incurred as a result of the pesticide administration. The inhibition might arise from biosynthetic pathway for amidopyrine N-demethylase e.g. at the level of □-aminolevulinic acid (□ALA) synthetase, the initial and rate-limiting step in the biosynthesis of mixed-function oxidase enzymes (Arizono *et al.* , 1993).

The present study reveal that glutathione S-transeferase was significantly increased after both single ($p<0.05$) and repeated ($p<0.001$) doses of deltamethrin. The present study also investigated the effect of deltamethrin on the levels of free radicals which were measured as thiobarbituric acid-reactive substances (TBARS). These levels were enhanced ($p<0.001$) after treatment of male mice with repeated doses of deltamethrin (Table 1).

Glutathione S-transeferase represents a family of enzymes or binding proteins identified in a variety of species and tissues. These enzymes are known to catalyze the conjugation of reduced glutathione with numerous compounds carrying an electrophilic center as the first step in the mercapturic acid formation (Hsu, 1981). They also function as binding proteins for compounds such as bilirubin and numerous carcinogens that don't serve as substrates. Previous studies have shown that reduced glutathione (GSH) level and glutathione S-transeferase activity can reduce the covalent binding of the activated forms of well known carcinogens (Sheweita and Tilmisany, 2003).

The present study also investigated the effect of deltamethrin on the levels of free radicals which were measured as thiobarbituric acid-reactive substances (TBARS). This study clearly demonstrated that deltamethrin significantly enhanced lipid peroxidation in the microsomal membrane and led

to peroxidation of cell membrane and also the release of toxic substances generated from lipid peroxidation. Lipid peroxidation in liver might be due to the breakdown of hydrogen peroxide (Halliwell and Gutterridge,1992, and Poeggeler *et al.* , 1993).

To sum it up, results derived from the present study seem to indicate that deltamethrin altering the hepatic microsomal enzyme activities. Careful application should be considered when using pyrethroid in broad scale to public health in houses and agriculture.

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تأثير مبيد دلتاميثرين على إنزيمات أيض العقاقيرفي كبد ذكور الفئران

صباح جابر البنا

قسم الدراسات البيئية – معهد الدراسات العليا والبحوث – جامعة الإسكندرية

يهتم هذا البحث بدراسة تأثير معاملة الحيوانات حقنا بالفم بمبيد دلتاميثرين (١٠ مجم/ كجم من وزن الجسم يوميا) لمدة ٢٤ ساعة كجرعة فردية أو جرعات متكررة لمدة ٧ أيام". تم تقدير محتوى الكبد من البروتين الميكروسومى، سيتوكروم P450، b5، ونشاط إنزيمات NADPH سيتوكروم C ريدكتيز، أميدوبيرين- N - ديميثيليز، أنيلين-٤- هيدروكسيليز، جلوتاثيون- S- ترانسفيريز ومستوى المواد المنشطة لحمض ثيوباربيتيورك (TBARS).

أشارت النتائج المتحصل عليها إلى أن الجرعة الفردية من دلتا ميثرين لم يكن لها تأثير معنوي على محتوى البروتين الميكروسومى بالكبد، سيتوكروم ب٥، أميدوبرين ن ديميثيلبز، أنيلين-٤-هيدروكسيليز ومستوى المواد المنشطة لحمض الثيوباربيتيورك (TBARS). بينما انخفض نشاط إنزيم سيتوكروم ب.٥، معنويا ($P<0.05$) وزاد نشاط إنزيم NADPH سيتوكروم C ريدكتيز ($P<0.001$)، وجلوتاثيون-S- ترانسفيريز ($P<0.05$). بينما الجرعة المتكررة لمدة سبعة أيام من الدلتاميثرين سببت انخفاضا معنويا في البروتين الميكروسومى ($P<0.05$) وكذلك اميدوبيرين -N- ديميثيليز ($P<0.001$). وزيادة معنوية ($P<0.01$). في نشاط الإنزيمات الأخرى التي درست.

وقد بينت هذه الدراسة أن الجرعة الفردية والمتكررة من مبيد دلتاميثرين لها تأثير واضح على إنزيمات أيض العقاقير بالكبد.