Influence of Permethrin and Cypermethrin on behavior in the mouse

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Abstract

Permethrin and Cypermethrin are synthetic pyrethroids, belonging to a group of insecticides with low mammalian toxicity and high insecticidal activity. The present study evaluated sub-acute toxicity of dermally administrated permethrin and cypermethrin in mice. Behavioral examination included assessments of lethality, weight gain, grooming, analgesymetry, anxiety, grasping, motor activity, and despair in response to inescapable swim stress. The study was conducted on 70 adult male mice, which were exposed dermally via the whole tail zone for 10 s once daily for 28 consecutive days at concentrations of 0%, 0.1%, 1% and 10% of each compound. No significant changes were observed in body weight gain, grooming behavior or pain sensation among the treated and control groups. However, the following effects were observed in the experimental groups: a tendency towards increased motor activity compared to controls (47% in P0.1% group, $P = 0.025$), a tendency to lose grasping faster than controls (48% and 40% decreased in P10% and C1% groups, respectively, ($P < 0.05$), shorter stay in the long arms and longer stay in the short arms on the elevated plus maze task compared to controls (up to 84% difference , $P < 0.05$), and failure in terms of floating on the inescapable swim stress task (500% and 900% increase in interruption times in the P10% and C10% groups, respectively, $P < 0.05$). In conclusion, upon long-term dermal exposure, synthetic pyrethroids may lead to increased motor activity, decreased grasping tendency and/or ability, increased apathy, and increased despair in the mouse animal model.

Introduction

Synthetic pyrethroid insecticides have been widely used in agriculture and domestic homes for over three decades and account for approximately 25% of the worldwide insecticide market. The actions of pyrethroid insecticides have been divided into two types (I and II) based on neurophysiologic effects and symptoms. Generally, the two types can be distinguished structurally by the presence (type II) or absence (type I) of an alpha-cyano substituent (Casida and Quistad, 1998; Laurence and Casida, 1983; Verschoyle and Aldridge, 1983). The acute mammalian neurotoxicity of pyrethroids has been well characterized, and several comprehensive reviews of pyrethroid toxicity and actions are available (De, 2001; Narahashi, 2001; Shafer *et al*., 2005).

Permethrin, a type I pyrethroid, provides insecticidal activity for several weeks following a single application and is used to control fleas, flies, mites, and cockroaches. Permethrin causes modification of sodium channels leading to prolonged depolarization and repetitive discharges in presynaptic nerve fibers after a single stimulus (Abou-Donia *et al*., 2004; Bloomquist, 1996; Narahashi, 1985). Cypermethrin is an active, type II, alpha-cyano pyrethroid which induces long-lasting trains of repetitive nerve impulses. It causes intense repetitive activity in the peripheral nerves which may lead to frequency-dependent depression of the nerve impulse. The major effect of pyrethroids is to delay the closing of the sodium channel, so that a prolonged sodium tail current persists after the membrane repolarization (Perger and Szadkowski, 1994; Vijverberg and Van den Bercken, 1982; Vijverberg and Van den Bercken, 1990).

There is insufficient information regarding the potential effects of pyrethroids on certain aspects of behavior both in humans and in animal models. The aim of the present study was to evaluate the effects of adult mice exposure to selected pyrethroids via the most natural contact route, i.e. dermal exposure. The reason to use permethrin and cypermethrin were: firstly, they are used frequently here in Iran and, secondly, each belongs to a different class of pyrethroids.

Procedure

Animals

Seventy adult, male mice (weighing 20-25 g) were used in this study. They were fed with commercial chow and tap water *ad lib*, and kept at room temperature with 12 h artificial light in 24 h.

Experimental protocol

Animals were divided into seven groups, with 10 animals in each. Once daily for 28 successive days, animals were exposed via their entire tail for 10 sec to one of the following solutions: water (0%), permethrin 0.1% (P0.1%), permethrin 1% (P1%), permethrin 10% (P10%), cypermethrin 0.1% (C0.1%), cypermethrin 1% (C1%), or cypermethrin 10% (C10%). Various tests were performed 24 h after ceasing the last treatment on Day 29.

Motor activity assessment

Animals were placed on a flat, round surface with a diameter of 50 cm and divided by two stapled lines into four equal sections. The number of crossings across the lines during 5 min was counted and recorded for each animal as an evidence of motor activity.

Grasping behavior

Animals were positioned on an inclined, wooden brushed surface with a 55° angle. The time the animals were able to keep grasping on to the surface was recorded.

Grooming behavior

A small amount of tap water was sprayed on to the chest of the animals. The number of licks during 5 min was counted and recorded for each animal.

Elevated plus maze (EPM) test

Animals were placed for 5 min on a standard elevated plus maze. The duration spent on short arms and long arms was recorded.

Hot plate test

A standard pharmacology hot plate (ATS Company, Tehran, Iran) was set at 58°C and the mice were placed on the instrument for up to 20 s. The time required for the animal to start licking its paw was taken as "pain sensation time". The time taken for the animal to start trying to jump out of the instrument was considered as the "pain tolerance time".

Floating behavior

Mice were placed in a bucket of water. The height of the water and the bucket were 30 cm and 50 cm, respectively. The number of swimming stops (i.e. floating behavior) during 2 min was recorded.

Chemicals

Commercial grade permethrin (25% w/v stock solution) and cypermethrin (10% w/v stock solution) were products of Partonar Company (Tehran, Iran).

Statistical analysis

Data are presented as means SEM. Differences between groups were analyzed using one-way ANOVA. When $P<0.05$, data were compared group by group with Bonferroni's t-test (a post-ANOVA test). P-value less than 0.05 was considered a statistically significant difference.

Results

General health and mortality

There were no significant differences in weight gain between control and treated animals during the study, thus eliminating considerable alteration in general health which may confound results. Six out of 10 mice treated with C10% died within 8 days of commencing the experiment, making a significant decrease in the life span of this group compared to the control (vehicle-treated) animals ($P < 0.05$, Table 1).

Motor activity

Control animals crossed the lines an average of 49.75 ± 8.20 times in 5 min. There was a tendency to increase line crossing in all treated groups, with the exception of the C10% group which showed a decrease in motor activity. However, only the P0.1% group showed a significant difference to control animals, with a 47% increase ($P = 0.025$, Table 1, Figure 1).

Grasping behavior

In most cases of the permethrin and cypermethrin-treated animals, there was a tendency to lose grasping

Table 1: Effects of topical exposure with pyrethroid pesticides on selected behavioral parameters in the mouse[1]

parameters	Control (8)	Permethrin[2]			Cypermethrin[2]		
		0.1% (9)	1% (10)	10% (9)	0.1% (9)	1% (7)	10% (4)
Activity (# line crossing / 5 min)	49.75±8.20	73.33±5.12*	61.20±6.83	55.56±4.22	58.40±5.66	50.57±10.92	39.50±9.77
Grooming (# in 5 min)	1.63±0.73	2.38±0.97	1.50±0.63	2.67±0.85	3.00±0.40	0.71±0.39	1.00±0.47
Long arm EPM (sec / 300 sec)	218.75±11.40	230.56±14.16	212.80±14.20*	175.78±14.18	250.10±10.53	180.71±23.12	150.50±18.07*
Short arm EPM (sec / 300 sec)	81.25±11.40	69.44±14.16*	87.20±14.20	124.22±14.18	52.60±9.36*	112.14±21.10	149.50±18.07
Grasping (sec)	4.85±0.68	3.36±0.52	3.80±0.69	2.49±0.81*	4.67±0.98	2.89±0.57*	5.58±1.42
Heat pain sensation (sec)	6.88±0.65	6.44±0.26	6.40±0.77	7.44±0.53	7.00±1.22	5.29±0.51	5.50±0.58
Heat pain tolerance (sec)	20.00±0.00	16.22±1.28	20.00±0.00	19.11±0.62	20.00±0.00	18.29±1.22	20.00±0.00
Despairing in floating (# in 5 min)	2.00±1.26	2.88±0.37	3.70±1.18	12.00±1.92*	3.30±1.32	0.57±0.32	21.00±2.05*

Data are presented as mean ± SEM

[1] Number of animals per group are shown in the bracket of the corresponding concentration. At the start, all groups consisted of 10 male, adult mice. [2] Treatment was applied topically to the tail for 10 s, once daily, for 28 consecutive days, and measurements were conducted on Day 29.

* Significantly different from control group at $P \leq 0.05$.

faster than controls. The decrease in resistance time compared to control animals reached significance in the P10% and C1% groups, by 48% (P = 0.044) and 40% (P = 0.049), respectively (Table 1, Figure 2).

Grooming Behavior

No significant difference was observed among various treatment groups (Table 1).

EPM test

The animals treated with P10% and C10% spent significantly less time in the long arms compared with controls. The decrease was 19% in P10% group and 31% in C10% group (P < 0.05, Table 1, Figure 3A). Conversely, the time spent in the short arms was increased in P10% and C10% groups by 52% and 84%, respectively (Table 1, Figure 3B). Interestingly, the lowest concentrations of the chemicals had an opposite effect, i.e., decreased the staying time in the short arms (P < 0.05).

Hot plate test

No significant difference was observed among the various treatment groups (Table 1).

Floating behavior

The animals treated with P10% and C10% stopped swimming more frequently than controls. The increase

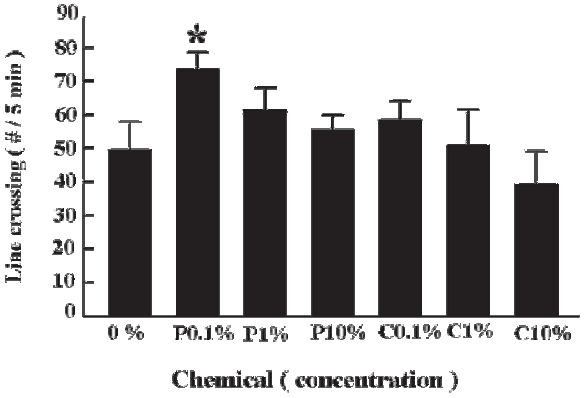

Figure 1: Effects on motor activity as a result of various concentrations of permethrin (P) and cypermethrin (C), compared to vehicle-treated animals (0) in the mouse. Chemicals were applied topically once daily for 28 successive days. * P0.1% decreased the parameter significantly (P = 0.025) compared to vehicle-treated animals. *n* = 4-10 per group

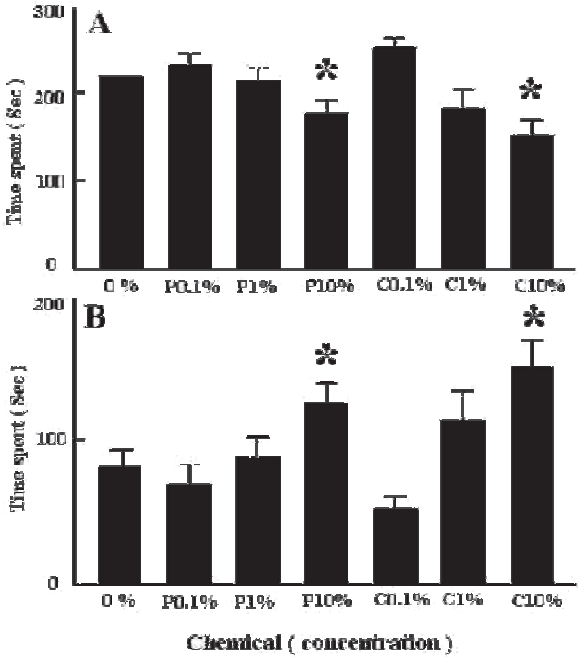

Figure 3: Effects of permethrin (P), cypermethrin (C), and vehicle (0) on the time spent by mice in the long arms (A) and short arms (B) of the EPM. Chemicals were applied topically once daily for 28 successive days. *Time spent in the long arms was shortened and the time spent in the short arms was increased by P10% and C10%, significantly (P < 0.05). *n* = 4-10 per group

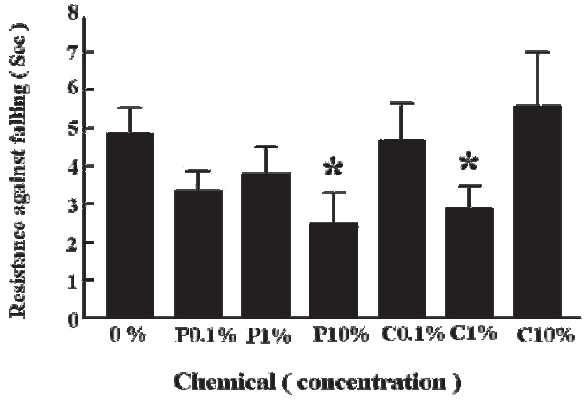

Figure 2: Effects on grasping at an inclined screen as a result of administration of various concentrations of permethrin (P) and cypermethrin (C), compared to vehicle-treated animals (0) in the mouse. Chemicals were applied topically once daily for 28 successive days. *The parameter was decreased significantly by P10% (P=0.044) and C1% (P = 0.049). *n* = 4-10 per group

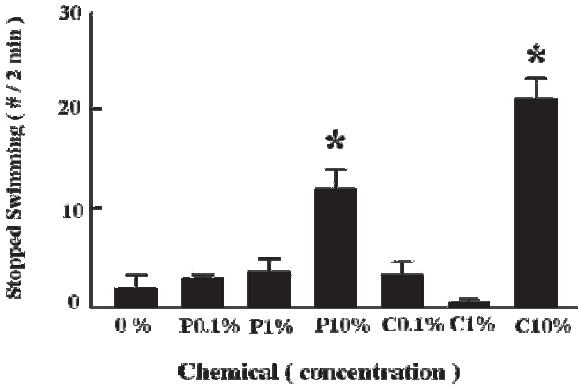

Figure 4: Despair in response to inescapable swim stress as a result of various concentrations of permethrin (P), cypermethrin (C), and vehicle (0) in the mouse. Chemicals were applied topically once daily for 28 successive days. * P10% and C10% increased despairing significantly (P < 0.05). *n* = 4-10 per group

was 500% in P10% group and 900% in P10% group ($P < 0.05$, Table 1, Figure 4). Furthermore, the increased demonstration of despair in all permethrin treated groups was dose-dependent.

Discussion

In this study, there were no significant changes in body weight gains in mice across all permethrin and cypermethrin treated groups in comparison to the control animals. Aldana and colleagues reported a statistically significant decrease (11%) in body weight, in i.p administration of 300 mg/kg cypermethrin to male rats for seven days (Aldana *et al*., 2001). However, some authors have reported that deltamethrin, a synthetic pyrethroid type II, has no significant effect on body weight. In this regard, our findings are consistent with the results from this laboratory.

In this study, six out of 10 mice treated with C10% died within 8 days of the experiment, resulting in a significant decrease in the life span of this group compared to the control (vehicle-treated) animals. Latuszynska et al. reported that chlorpyrifos and cypermethrin (administered in a mixture) strongly inhibited cholinesterase activity in plasma and acetylcholinesterase activity in brain, and had a toxic effect on the CNS. However, the effect of the mixture of pesticides on the CNS was not stronger than that caused by alpha-cypermethrin alone (Latuszynska *et al*., 2001). This wide variation observed in toxicity may reflect different mixtures of isomers in the materials tested. The ratio of cis/trans isomers affect toxicity and additives and impurities could also modify the effects. Based on the data from the literature, there is no doubt that cypermethrin exerts a neurotoxic effect which is manifested by an increase of cholinesterase activity and the impairment neural conductivity in the central and peripheral nervous systems.

Dose-dependent decreases in motor activity are consistent with a wide variety of previous reports on the acute effects of pyrethroids. Previous research work from this laboratory and others (Crofton *et al*., 1995; Crofen and Reiter, 1988; Gilbert *et al*., 1990; McDaniel and Moser, 1993) has demonstrated decreased motor activity for five of the currently tested compounds using the same test method. Decreases in motor activity have been demonstrated in other testing devices after acute or short-term exposure, including permethrin (Hoy *et al*., 2000), fenvalerate (De Souza Spinosa *et al*., 1999), cyhalothrin (Righi and Palermo-Neto, 2003), gamma-cyhalothrin (Ratnasooriya *et al*., 2002), and cypermethrin (Hornychova *et al*., 1995). The acute motor depressant effect has been also observed in mice after oral exposure to fenvalerate (Mandhane and Chopde, 1997) and deltamethrin (Chanh *et al*., 1984). However, there are a few reports of acute pyrethroid exposures resulting in increased motor activity. Increased motor activity was reported in mice acutely exposed to commercial formulations of fenvalerate and permethrin (Mitchell *et al*., 1988). Husain et al. found an increase in motor activity 1 day after 15 day exposure to a deltamethrin formulation. Such reports of increased activity are difficult to interpret and may have resulted from unknown factors in the commercial formulations used (Husain *et al*., 1996). The present findings confirm that there is a tendency in all treated animals to increase motor activity. However, the only P0.1% group showed a significant difference to controls with a 47% increase.

Our results verify previous reports in the literature describing two different syndromes, i.e., aggressive sparring behavior, fine to whole-body tremor, hyperthermia, and decreased motor activity for type I pyrethroid permethrin, and pawing, burrowing, salivation, whole body tremor to choreoathetosis, hypothermia, and lowered motor activity for the type II pyrethroid cypermethrin. In addition, McDaniel *et al*. reported that permethrin produced decreased grip strengths, increased resistance to capture, increased reactivity to a click stimulus, and induced head and forelimb shaking and agitated behaviors. In contrast, cypermethrin produced pronounced neuromuscular weakness and equilibrium changes, retropulsion, lateral head movements, alterations in responses to various stimuli, and increased urination (McDaniel and Moser, 1993). Although there were similarities in some effects (e.g., decreased motor activity), the pesticides differed significantly in their overall behavioral profiles as well as in terms of severity and the time course of effects.

Our findings showed no significant difference among the various treatment groups in the grooming test. Latuszynska reported that the dermal application of alpha-cypermethrin in doses of 50 and 250 mg/kg did not lead to changes in the behavior of the rats in the open field test after two weeks of the experiment. However, after four weeks, grooming was increased only in rats treated with alpha-cypermethrin in a dose of 250 mg/kg (Latuszynska *et al*., 2001).

In our study, results showed that the animals treated with P10% and C10% spent significantly less time in the long arms of the EPM test compared with controls. The decrease was 19% in the P10% group and 31% in the C10% group. Conversely, the time spent in the short arms was increased in P10% and C10% groups by 52% and 84%, respectively. Interestingly, the lowest concentrations of the chemicals had the opposite effect, i.e., decreased the staying time in the short arms. This demonstrates that in high concentrations, there was a decrease in anxiety behavior. A chronic-toxicity study of permethrin was conducted in rats and mice by Ishmael and Lithfield (Ishmael and Lithfield, 1988). Groups of Alpk:AP

(Wistar-derived) rats were fed diets containing 0, 500, 1000 or 2500 ppm permethrin for 2 years and Swiss-derived mice were maintained for their lifetime (80% mortality) on diets containing 0, 250, 1000, or 2500 ppm permethrin. Changes of toxicological significance were confined to the top dose level of 2500 ppm permethrin in both species. Tremors and hypersensitivity to noise were noted in rats at this dose during the first 2 weeks of study but such signs were not seen in mice. Pathological examination of the central and peripheral nervous systems did not reveal abnormalities attributable to permethrin administration. Latuszynska's finding suggests that the repeated prolonged immobilization may cause stress leading to suppression of acetylcholinesterase in the brain and cholinesterase in plasma (Latuszynska *et al*., 2001). These studies did not clearly define anxiety behavior in the laboratory tests, but in our study, we defined the increase or decrease of anxiety as time spent in the short or long arms on the EPM.

In the hot plate test, there was no significant difference among all permethrin and cypermethrin treated groups in comparison with control animals. No other data in relation to this finding has been observed.

Based on our results, the animals treated with P10% and C10% stopped swimming more frequently than the control animals. The increase compared to controls was 500% in P10% group and 900% in P10% group. Furthermore, increase in despair behavior in all permethrin treated groups was dose-dependent. Reduction in swimming performance has been referred to as "behavioral despair", which may be considered as an acute depressive reaction in response to inescapable swim stress (Porsolt *et al*., 1978; Porsolt *et al*., 1979). Farag showed that exposure of F0-mice to permethrin in the dose groups of 9.8 and 19.6 mg/kg/d before mating, caused a decrease in the performance of reflexes, swimming behavior, and locomotion frequencies in the F1-mice in the open field (Farag *et al*., 2006). Therefore we can argue that dermal administration of permethrin and cypermethrin can cause various effects. Low concentrations may lead to decrease and high concentrations may lead to increase in despairing behavior.

Conclusions

The aim of the present study was to evaluate the effects of exposure to selected pyrethroids on adult mice via the most natural contact route, i.e. dermal exposure. The overall results of this study clearly demonstrate that dermal administration of permethrin and cypermethrin leads to behavioral changes in the mice. Low toxicity of pyrethroid insecticides for mammals is explained by their rapid biotransformation and discharge in urine. Although extrapolation from mice to humans should be conducted with caution, one may conclude on the basis of our data that permethrin and cypermethrin usage may cause hazardous effects at various levels to non-target organisms, including human beings. In the absence of advanced behavioral studies, we recommend safety precautions in relation to handling pyrethroids.

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