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Effects of dermal sub-chronic exposure of pubescent male rats to permethrin (PRMT) on the histological structures of genital tract, testosterone and lipoperoxidation

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ABSTRACT

Short-term effects of pyrethroids on human health are better and well identified, whereas long-term risk's estimation remains difficult, especially those affecting the reproductive function. The present study, carried out in male rats, is a contribution to explore some effects underlying permethrin (PRMT) toxicity. The aim of the present work was to investigate the effect of different subcutaneous treatments with PRMT low doses on testes and epididymides histopathology, testosterone and oxidative stress in pubescent male rats. Groups of six animals were treated with a dermal daily dose of 0.013, 0.13, or 1.3 mg/kg b.w/day of PRMT in 70% ethanol for 30, 45, and 60 days, respectively.

Macroscopic studies showed an influence of PRMT on the testes, the epididymides and body weight. The pyrethroid induces a testis disturbance traduced by a deregulation of spermatogenesis and an epididymis dysfunction by the appearance of strong deformations into the microstructure of the epididymides. A hormonal disruption was evidenced by the measurement of the plasma testosterone concentrations. The findings of the present investigation mentioned a significant increase ($p \leq 0.05$) in lipoperoxidation, after 45 or 60 days, when we measured the plasma malondialdehyde (MDA) concentrations.

In conclusion the study shows that subcutaneous PRMT treatment causes an arrest of spermatogenesis, and a significant disharmony in testosterone concentration and MDA levels. These effects are related to dose, length of treatment and to the lipid peroxidation, which may be one of the molecular mechanisms involved in PRMT-induced gonads and epididymides toxicity.

Contents

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1. Introduction

Pyrethroid insecticides are considered as a class of agents that act on many targets in the organisms of animals and in particular the mammals. Their capacity to interact reversibly with a wide range of ion channels, possibly via their phosphorylation state, is a key property of pyrethroids, and sodium channels are their major target (Davies et al., 2007; Narahashi et al., 2007; Peterson et al., 2008). These classes of insecticides are extensively employed throughout the world as wide-spectrum products for numerous crops and for indoor pest control in the public health sector and housing (Costa et al., 2008; Bjorling-Poulsen et al., 2008). In the last decade, many veterans of the Persian Gulf War have complained of chronic symptoms including headache, loss of memory, fatigue, muscle and joint pain, and ataxia. Moreover the majority of the symptoms reported by the affected veterans involve abnormal regulation of functions in either the central or peripheral nervous system or both (Abdel-Rahman et al., 2001). In this context, Abou-Donia et al. (2001a,b) mentioned that recent studies have suggested significant sensorimotor deficits and blood–brain barrier disruption following exposure to *N*, *N*-diethyl *m*-toluamide (DEET) and PRMT alone or in combination. They conclude that sub-chronic exposure to these pyrethroids experienced by service personal during the Persian Gulf War has played an important role in the development of illnesses in some veterans after the Gulf War.

PRMT is a type I synthetic pyrethroid insecticide that exists in four different stereoisomers. It is (1RS, 3RS, 1RS, 3SR)-3-(2, 2- dichloroethenyl)-2, 2- dimethylcyclopropane carboxylic acid (3-phenoxyphenyl) methyl ester (Casida et al., 1983). This toxic is considered as the main active molecule of many commercial insecticides that have several trade names such as Ambush, Ectiban, Pounce, Prelude, etc.

This pyrethroid is efficient against a large number of harmful insects (Ben Cheikh, 1999). It presents an intensive adsorption to organic materials, it is heat resistant and more stable in acid medium than in basic one (IPCS, 1990). Some reports revealed that cis-PRMT is 10 fold more toxic than trans-PRMT in rats and mice (OMS, 1990). However the consequences of long-term exposure to this product are of concern.

So it appears that there is a real deficiency data concerning risks induced by PRMT low doses on male reproductive function and in particular on the stress oxidant due to daily chronic exposure. This ignorance often creates many worries because of the numerous harmful effects of PRMT on living beings when it is applied for a long term.

The objective of the present study was to investigate the effects induced by PRMT on the histopathology of the genital tract presented specifically by the testes and the epididymides. For this our study aims to examine and characterize the testicular and epididymal toxicity, which might be induced by exposure to low doses of PRMT. This was achieved by histopathological examination of whole testicular and epididymal sections obtained from male treated rats in comparison with male controls. At the same time, the plasma testosterone and MDA levels were evaluated after each experimental period. Our findings mention that subcutaneous treatment by PRMT produces a significant influence on plasma testosterone concentrations and lipoperoxidation by the measurement of the plasma MDA levels. The assessment of time and/or PRMT dose is investigated in order to obtain more data concerning the effects of this toxic on reproductive function in pubescent male rats.

2. Materials and methods

2.1. Chemicals

Permethrin (±)-cis-3-(2, 2-dichloroethyl)-2, 2-dimethylcyclopropane carboxylic acid (3-phenoxyphenyl) methyl ester was obtained from Dr. Ehrenstorfer Gmbh. D-86199 Angsburg, Germany.

The immuno-radiodetection kit of testosterone (DSL-4000 ACTIVE) was provided from Biopartener.

2.2. Animals

Male rats of Wistar strain (230–250 g), aged 4 months obtained from SIPHAT, Tunis (Tunisia), were used. Animals were randomly assigned to control (3 groups, each of 6 individuals) and treatment groups (3 groups, also of 6 individuals each) and housed at 21 ± 5 °C with a 12 h light/dark cycle and 55% humidity. Diets and water were given *ad libitum* to rats. Animals were maintained during the experimental period in accordance with guidelines for animals' care of the "Faculté de Médecine de Monastir", Tunisia.

2.3. Dermal application of permethrin

- The treatment was realized according to the protocol described by Abou-Donia et al. (2001a,b). The pubescent male rats were randomly divided into six groups each comprising six animals.
- Group I (low dose PRMT group): Rats were fed with commercial pelleted feed *ad libitum* and injected subcutaneously with PRMT (0.013 mg/kg/day) during 30 days.
- Group II (medium dose PRMT group): Rats were fed with commercial pelleted feed *ad libitum* they were injected subcutaneously with PRMT 0.013 mg/kg/day and 0.13 mg/kg/day during 30 and 45 days, respectively.
- Group III (high dose PRMT group): Rats were fed with commercial pelleted feed *ad libitum* and injected subcutaneously with PRMT (0.013 mg/kg b.w/day); (0.13 mg/kg b.w/day) or (1.3 mg/kg b.w/day) during 30, 45 or 60 days, respectively.
- Group IV (control for groups I–III): Rats were fed with commercial pelleted feed *ad libitum* and obtained dermal