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PERMETHRIN-INDUCED DECREASE IN LIBIDO AND ANDROGEN LEVELS IN ALBINO RATS

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ABSTRACT

Permethrin, a type I pyrethroid, is known to interfere with hormonal levels in some studies. It decreased testosterone levels in mice by interfering with the functional integrity of the Leydig cell (Zhang et Al, 2007). It also reportedly exhibited anti-androgen effects in male rats (Xu et Al, 2008) and exposure of rats to Permethrin decreased sperm motility and overall quality (Yuan et Al. , 2010). Effect of Permethrin on libido in rodents was earlier reported in NMRI mice (Solati, et Al, 2009) in which both testosterone and libido were reduced. The current study was, therefore, undertaken to test the reproductive effects of Permethrin in the male albino rat, Rattus norvegicus to gather further evidence on Permethrin effects on reproduction in rodents.

INTRODUCTION

Permethrin is a pyrethroid insecticide. Pyrethroids are organic compounds that possess common characteristics with the naturally occurring pyrethrins extracted from pyrethrum flowers (*Chrysanthemum cineriariaefolium*) (Cox 2002, Roy 2002). They are majorly used in agriculture, forestry (Rossbach *et al.,* 2015) and household (Berger-Preiss *et al.,* 2002, Rohrer *et al.*,2003). They are also used in public health (WHO 2004), textile and commercial air crafts (Berger-Preiss *et al.,* 2004).

Permethrin is a type I pyrethroid which is used to kill noxious insects such as bodylice (Yoon *et al.*, 2003). It is also used in the medical treatment of scabies, a condition caused by mite that infest and irritate skin (Abedin *et al* ., 2007; Goldust *et al* ., 2012). In the tropical countries, mosquito nets are usually treated with permethrin to prevent malaria (Iyaniwura *et al.*, 2008). Permethrin is metabolized in the liver where it is broken down by the cytochrome P450 enzyme (Tange *et al*., 2014).

Permethrin affects the nervous system (Drago *et al*., 2014). It interacts with sodium channel through binding to sodium ions, blocking their movements which result in repetitive nerve impulses (Dong *et al*., 2013). At high doses the neurotoxic effects of permethrin include tremor (involuntary shaking of the body), depressed reflexes (Wolansky and Harril 2008), paresthesia, salivation tiptoe gait and splayed gait in rat. It also inhibit a variety of nervous system ATPase (Kakko *et al.,* 2003), resulting in increased release of the neurotransmitter acetylcholine, monoamine oxidase-A, the enzyme which regulates normal levels of other neurotransmitters and acetylcholinesterase, the enzyme that breaks down acetylcholine.

Additionally, permethrin inhibits a nervous system receptor, the GABA A receptor

(major inhibitory neurotransmitter *receptors* in mammalian brain), producing excitability and convulsion (Soderlund *et al*., 2012). At higher dose, permethrin inhibit the process by which complex food substances are oxidized with an accompanied release of energy (respiration). Permethrin is genotoxic, it causes an increase in chromosome aberrations, chromosome fragments and DNA damage (Tisch *et al.*, 2002, Hasan *et al*., 2012). It is also immunotoxic (Emara and Draz 2007).

Permethrin pose detrimental effect on reproductive hormones (Bian *et al.,* 2004). It exhibit estrogen like effect in female rats but antiandrogen–like effects in male rats (Xu *et al.,* 2008). Permethrin disrupts the production of testosterone in the body through the destruction of the membrane of mitochondria in leydig cells of adult male mouse (Zhang *et al*., 2007) and has disruptive effect on libido and plasma concentration of hormone produced in the gonad in adult male NMRI mice (Solati *et al*., 2009). It adversely affects semen quality in rats and reduces the motility of mature sperm cells (Yuan *et al.,* 2010). Hence, the current study is aimed at evaluating the effect of permethrin on gonadal function, these include its effect on plasma testosterone level, sexual behavior, testicular weight, circumference, seminiferous tubules and population of matured spermatozoa within the lumen.

Secondly it investigate the effect produced on the pups whose paternity were exposed to permethrin.

MATERIALS AND METHODS

Thirty mature male and twenty - one female sexually mature albino rats wing between 150 to 155g were randomly selected from the Animal House of the Department of Animal and Environmental Biology, University of Port Harcourt. They were maintained under standard laboratory conditions and provided with feed (Super Deluxe Animal Feed, Eastern Premier Feed Mill Company Ltd, Port Harcourt) and water *ad libitum*.

The males were randomly divided into three groups A,B, and C of 10 rats each. Groups B and C received 75mg and 150 mg/kg/day respectively of Permethrin (Longway Trading, Jintang City, Jiangsu, China) through gavage (Day 1) for 28 days. Group A which served as control, received the vehicle (Goya oil) only. On Day 21 seven females in proestrous were introduced into each group for mating and the behaviour of of the males in each group was noted.

Testosterone assay

On Day 28 of initiation of treatment, blood was collected in heparinized syringes and centrifuged for testosterone assay, using testosterone enzyme immuno assay according to the method of Tietz (1995).

Testicular weight and histopathological examination

On Day 28, the males were weighed and euthanized and the testes were surgically removed. The circumference of the testes were measured with a thread and a ruler, and the testes weighed using Metlar electronic weighing balance. Thereafter testes were dehydrated in graded ethanol and then infiltrated with xylene for 1 hour, embedded in paraffin and sliced at 10 µm thickness with a microtome. Following hematoxylin and eosin staining, sections were examined with the light microscope (Research Photomicrographic Microscope, Olympus Co., Japan).

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Examination of Pups

Pups were physically examined, the length measured with a thread and metre rule and then weighed with the electronic balance.

Statistical Analysis

Data for testosterone, testicular weight and circumference, litter weight and size were presented as means ± SEM and analyzed by ANOVA. Where a significant F was found, mean separation test was performed using Turkey's test.

RESULTS

Results indicated that Permethrin decreased testosterone level in group C that received 150mg/kg/day permethrin at the end of the first week though the difference was not significant. At the end of the second week, mean testosterone was significantly lower in groups B and C than in Control group (group A). Mean hormonal levels were further significantly depressed at the end of the third week in both groups B and C. Mean serum testosterone in group C was 1.87± 0.01ng/ml compared to the mean level of 3.89±0.01ng/ml, $P \leq 0.05$.

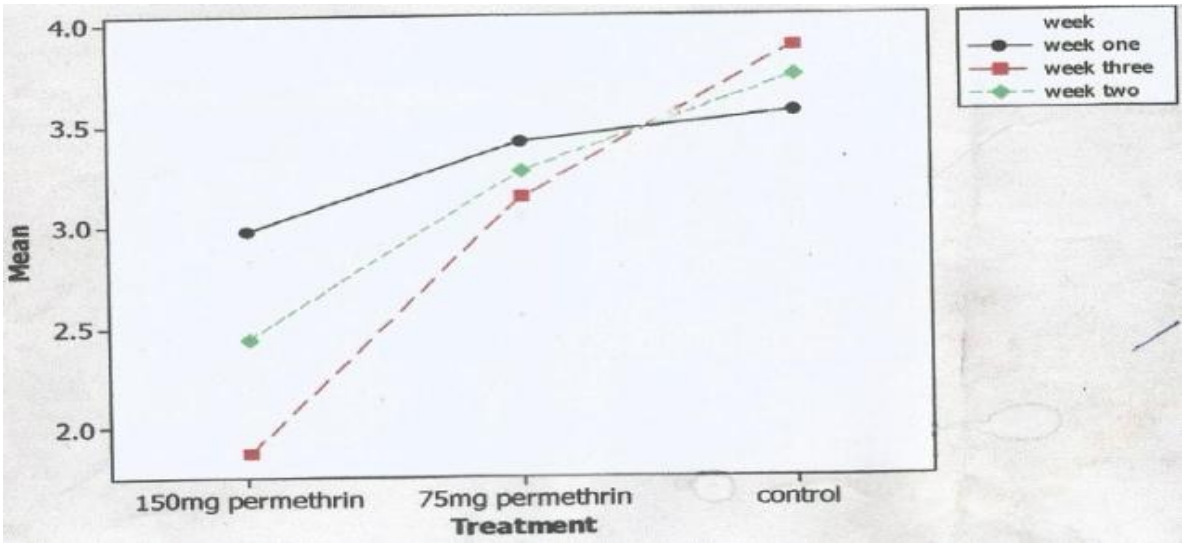

Figure 1: Interaction plot (data means) for testosterone level

Effects of Permethrin on Sexual behaviour, Testicular weight and Circumference

Observation of males treated with 75 and 150mg/kg/day showed that the male avoided the female when the female was presented to each of them (Figs 1A and 1B) compared to the response of males from group A (control) in which the male goes after the female.

Mean testicular weight of group B (1.27± 0.00) and group C (1.24± 0.00) were not significantly different from those of the corresponding value for control animals (1.30± 0.00) (Fig. 2). Mean testicular circumference (cm) of group B (4.80± 0.02) and C (4.77 ± 0.00) were not significantly different from that of Control group (4.88 ± 0.00), $P \leq 0.05$, (Fig. 3).

Plate 1A: Photograph of the male albino rat of the control group showing normal sexual behaviour in which the male goes after the female. Yellow arrow points at the male while red arrow points at the female.

Plate 1B: Photograph of the male albino rat exposed to 75mg/kg/d permethrin showing sexual dysfunction in which the male avoids the female. Yellow arrow points at the male while red arrow points at the female.

Plate 1C: Photograph of the male albino rat exposed to 150mg/kg/d permethrin showing sexual dysfunction in which the male avoids the female. Yellow arrow points at the male while red arrow points at the female.

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Effects of Paternal Exposure to Permethrin on Weight and Length of Pups

Mean weight of pups whose paternity were exposed to 75 and 150 mg/kg/day (4.22 ± 0.04 and 4.49 ± 0.06, respectively) were not significantly different from that of Control animals (4.53 ± 0.08) (Fig.4).

Similarly, paternal exposure to Permethrin did not cause any obvious anatomical effect on the pups. The mean size of pups whose paternity received either 75mg/kg/day or 150 mg/kg/day were 6.58 ± 0.03 and 6.69 ± 0.06 were not significantly different from the control of 6.89 ± 0.07, $P \leq 0.05$. Physical examination of each pup did not show abnormalities, physical deformities, or lesions.

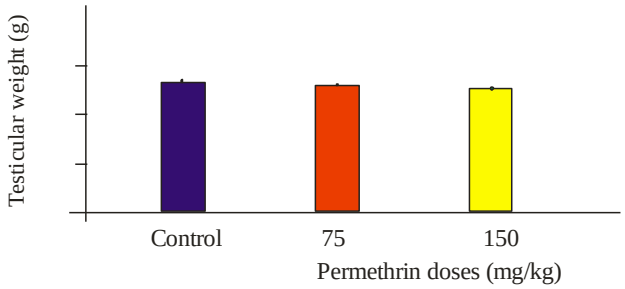

Figure 2: Effect of Permethrin on Testicular weight (g)

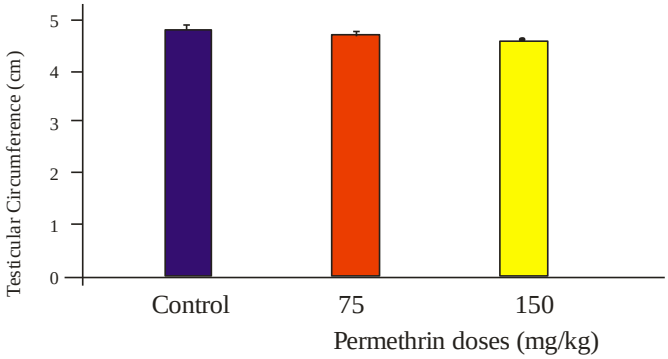

Figure 3: Effect of Permethrin on Testicular Circumference (cm)

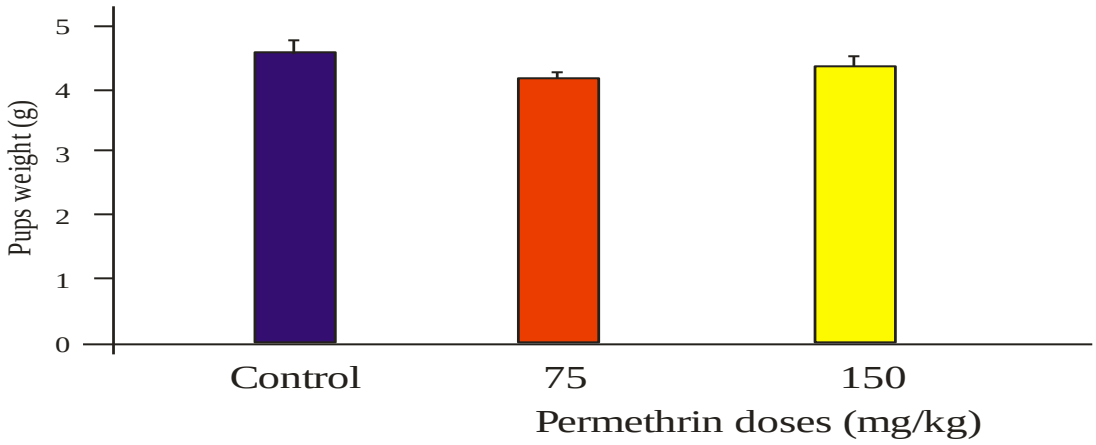

Figure 4: Effect of Paternal Exposure to Permethrin on Pups Weight

Histopathology of the Testes

Permethrin-treated animals but not control group showed marked alteration of seminiferous tubules in form of wider lumen and reduced population of mature sperm (Plates 2B and 2C and 2A). The control group A photomicrograph showed normal structure of the tubule and a good population of matured spermatozoa within the lumen (Plate 2A, H& E x100).

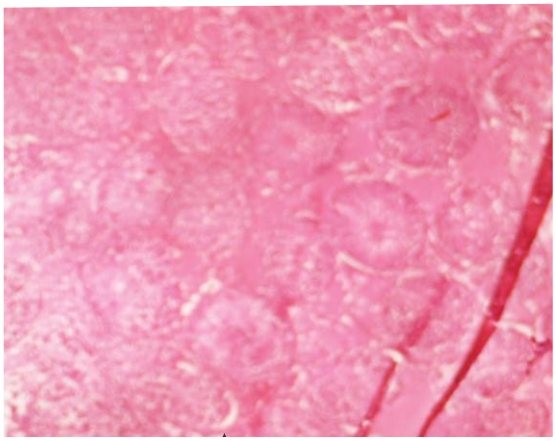

Plate 2A: Photomicrograph of the rat testis in the control group A showing normal structure of the seminiferous tubules and good population of matured spermatozoa within the lumen H&E x 100.

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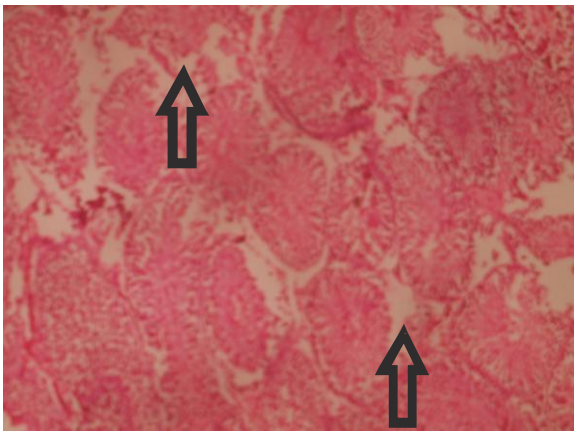

Plate 2B: Photomicrograph of the seminiferous tubules of rat testis in the group B administered 75mg/kg/d permethrin showing alteration of seminiferous tubules H & E x 100.

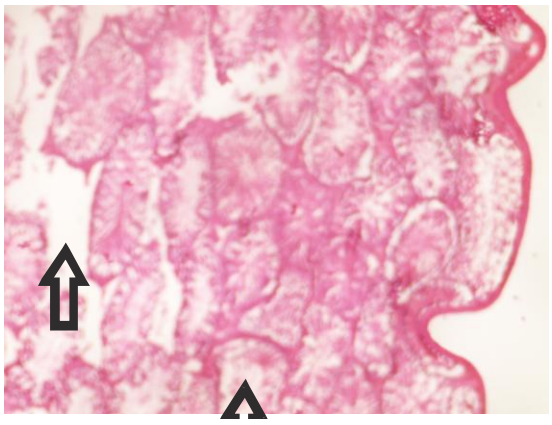

Plate 2C: Photomicrograph of the rat testis in the group C administered 150mg/kg/d permethrin showing alteration of seminiferous tubules, wider lumen and reduction of matured spermatozoa within the lumen H & E x 100

DISCUSSION

This study showed that a prolonged treatment of male rats (28 days) by gavage r significantly reduced the level of testosterone in a dose dependent manner. The reduction in hormonal level was was also time dependent, giving a time versus dose interaction. This agrees with the report of Zhang *et al* (2007) that Permethrin destroyed the biosynthesis of testosterone in adult male mice through destruction of the Leydig cell mitochondrial membrane. Decreased synthesis of testosterone in the rat by Permethrin has earlier been reported in the rat (Elbetieha, *et al*. 2001).

Hauet *et al* (2005) suggested that cis-permethrin decreases testosterone biosynthesis probably by blocking the transportation of cholesterol into the mitochondria for steroid synthesis. They reported that LH-stimulated steroid synthesis stimulated by intercellular cholesterol transport into testis mitochondria

was inhibited by Permethrin (Hauet *et al*, 2005). Furthermore, Permethrin down - regulated peripheral-type benzodiazepine receptors abundant in mitochondrial outer membrane in steroidogenic cells and inhibited the activity of steroidogeneic acute regulatory protein (StAR) (Zhang, *et al*. 2007) which plays a very important role in steroidogeneic. Jin et. al. (2012) also reported that exposure to some pyrethroid significantly decreased activities of enzymes involved in the synthesis of testosterone and reduced the Level of testosterone.

The current study is, perhaps, among the first to establish that permethrin-induced decrease in testosterone is accompanied by a decrease in libido in the rat as shown in Plate IB and IC compared to the control group. Isidori, *et. al*. (2005) earlier reported decreased sexual activities in men associated with decreased testosterone and Solati *et al*. (2005) also reported that Permethrin induced decrease in testosterone lowered the libido of treated NMRI mice. It is also well established that testosterone is needed for the manifestation of libido in the male (Bancroft, 2005). It is likely that the Permethrin-induced decrease in testosterone may have decreased the libido of these rats.

Gamma-Aminobutyric Acid (GABA), an inhibitory neurotransmitter tends to lower neuronal excitability throughout the nervous system (Paredes and Agmo, 1992) and suppresses sexual drive and erectile response in animals. (Fernandez *et al*., 1990). Type II pyrethroid are known to activate GABA receptors and may also induce libido this mechanism.

Exposure to Permethrin also decreased testicular weight at the two doses of 75 and 150 mg/kg/day but this was not significant. Effects of permethrin on testicular weight is conflictive. Zhang *et al*. (2007) reported similar finding thats that permethrin-induced decrease in testicular weight after six weeks of treatment was not significant. Jin *et al*. (2012) and Omotoso *et al*. (2014) however reported a significant decrease testicular weight with Permethrin administration in mice. These differences may be due to the dosages used. Testicular circumference also was not significantly affected by Permethrin treatment in our study (Fig. 3).

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