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LAMBDA CYHALOTHRIN INSECTICIDE INDUCED DNA DAMAGE AND HISTOPATHOLOGICAL CHANGES IN BRAIN AND LIVER OF SPRAGUE DAWLEY RATS.

Doha Yahia[1] and Marwa F. Ali[2]

[1] Department of Forensic Medicine and Toxicology, Faculty of Veterinary Medicine, Assiut University, Egypt.

[2] Department of Veterinary Pathology and Clinical Pathology, Faculty of Veterinary Medicine, Assiut University, Assiut, Egypt

ABSTRACT

Lambda-cyhalothrin (LCT) is a type II pyrethroid insecticide used all over the world. The current study aimed to investigate DNA damage induced by LCT in brain and liver tissues of Sprague dawley rats and its relation to the oxidative stress, in addition to exploration of histopathological changes in these organs. Thirty adult male rats were used in the study and classified into three groups, 10 animals in each group. The first group was orally exposed to one third LD50 of LCT (Dolf 2.5% EC) for 24 hours, the second group was exposed for 48 hours and the third group was left as control and received corn oil only. Animals were euthanized by diethyl ether anesthesia, blood samples were collected from descending aorta, brain and liver samples were used for comet assay and histopathological examination. Results revealed that acute exposure of rats to LCT caused abnormal gate and hind limb paralysis in some animals, induced oxidative stress through increased level of Malondialdehyde (MDA) and decreased level of glutathione peroxidase (GPx) in serum, extensive DNA damage in brain and liver at 24 and 48 hours indicated by increased tail length, % of DNA in tail, tail moment, and olive tail moment. Histpathological changes in cerebrum, cerebellum and liver tissues. It can be concluded that LCT pyrethroid insecticide has the potential to cause genotoxic effect through DNA damage in brain and liver. The study also confirms that comet assay is an appropriate and sensitive method for assessment of genotoxicity resulting from exposure to pesticides.

Key words: *Lambda cyhalothrin, DNA damage, Comet, brain, liver, oxidative stress.*

INTRODUCTION

Pyrethroids are widely used in the field of pest control and household use as well as veterinary medicine and are among the most known potent insecticides (Smith & Stratton, 1986). Lambda-cyhalothrin (LCT) is a synthetic type II pyrethroid insecticide excessively used worldwide to control a wide range of insects in a variety of crops (Campana *et al.*, 1999). It is also used for the control of a broad range of ectoparasites especially on cattle and sheep (Abd Elkawy *et al.*, 2013). The harmful effects of many pesticides, such as organochlorines, organophosphates and carbamates, have led to the use of pyrethroids as alternatives (Celik *et al.*, 2005) due to their high efficacy, easy biodegradability, and low

toxicity to birds and mammals (Kale *et al*., 1999). LCT has a neurotoxic effect through voltage-dependent sodium channels (Soderlund *et al.*, 2002; Ray & Fry, 2006) it also affects chloride and calcium channels that are important for proper nerve function (He *et al*., 2008).

Pesticides are known to produce oxidative stress, and several studies suggest that oxygen free radical formation can be a major contributor to the toxicity of pesticides (Monteiro *et al*., 2006; Modesto & Martinez, 2010; Lee *et al*., 2017). The generation of reactive oxygen species (ROS) induces damage to the various membranous components of the cells (Bebe & Panemangalore, 2003). Damage to membrane lipids, lipid peroxidation, is considered as one of the molecular mechanisms involved in pesticide toxicity and its predictive importance as a biomarker for oxidative stress is indicated in different investigations (Kavitha & Rao, 2008; Ballesteros *et al.*, 2009).

The lipophilic nature of pyrethroid insecticide such as lambda-cyhalothrin has been found to accumulate in biological membranes leading to oxidative damage (Michelangeli *et al.*, 1990). Malondialdehyde (MDA) is used as a convenient biomarker for lipid peroxidation and it is one of the most reliable and popular markers to determine oxidative stress in clinical situations (Ayala *et al*., 2014; Arce *et al*., 2017). LCT induced genotoxicity, micronucleus formation and chromosomal aberrations in rat bone marrow cells (Fahmy & Abdallah, 2001; Celik *et al.*, 2003, 2005) and in human lymphocytes cultured *in vitro* (Naravaneni & Jamil, 2005).

The alkaline single cell gel electrophoresis (SCGE) which is known as comet assay is a rapid and sensitive method used for quantitating DNA lesions in mammalian cells (Singh *et al.*, 1988; Tsuda *et al.*, 1998). It is used to detect different types of DNA damage such as single and double strand breakage and alkali-labile sites in any nucleated cell. The significant advantages of the comet assay over other genotoxicity tests are its fairly straight forward technique, sensitivity, requirement for small numbers of cells and rapid production of data (Tice *et al.*, 2000).

Brain is the main target organ for LCT toxicity while the liver is responsible for detoxification of almost all xenobiotics that reach the body through oral route. Therefore, the present study aims to investigate the oxidative stress and genotoxic effect of acute toxicity with LCT as well as histological changes in brain and liver tissues.

MATERIALS AND METHODS

CHEMICALS

A commercial formulation of synthetic pyrethroid lambda-cyhalothrin 2.5 gm/100ml, named Dolf 2.5 EC (Star Chem co., Egypt) was used in the study.

ANIMALS AND TREATMENTS

Thirty Sprague-Dawley adult male rats, weighing between 100 and 120 g, were obtained from the Animal Laboratory House of Faculty of Medicine Assiut University, Assiut, Egypt. The animals were housed in plastic cages and allowed to acclimatize to the new environment for a week before the experiment. Rats were fed on standard food pellets and tap water ad libitum. The rats were housed at 24–25 ◦C and in a daily dark/light cycle. The design of the study was in accordance with the ethical guidelines of experimental animals handling and use. The animals were randomly divided into three groups, 10

animals per group. The first group was exposed to one dose of LCT 26 mg/kg body weight which represents one third of LD_{50} (79 mg/kg Body weight) according to Southwood (1985) by oral gavage these animals were sacrificed after 24 hours. The second group received two doses of LCT and sacrificed after 48 hours. The third group was left as control and exposed to corn oil.

NECROPSY

Animals were anaesthetized by diethyl ether and blood samples were collected from descending aorta for determination of lipid peroxide (MDA) and antioxidant (GPx). Brain and liver samples were collected and divided into two portions; one of them was used for comet assay and the other was fixed in 10% formalin solution, dehydrated, and embedded in paraffin. Sections were cut and stained with hematoxylin and eosin (H&E) for histological examination.

Determination of serum malondialdehyde level (mda)

Determination of serum MDA was done by a spectrophotometric means (UV spectrophotometer, Optizen 3220 UV, Mecasys Co. Ltd, Korea) according to Grotto *et al.* (2009) by using colorimetric kit supplied by Bio-diagnostics (Dokki, Giza, Egypt).

Determination of serum glutathione peroxidase (GPx) activity

Measurement of glutathione peroxidase activity in serum samples was done using test kits supplied by Bio-diagnostic (Dokki, Giza, Egypt) by UV spectrophotometer (Optizen 3220 UV, Mecasys Co. Ltd, Korea) and according to the method of Abd Ellah *et al.* (2004).

Comet assay (Single cell gel electrophoresis)

Comet assay was performed according to Sassaki *et al* (1997), on brief frosted Slides were lined by double layer of normal agarose 1% then the nuclei isolated by homogenization of a small piece of brain or liver in 1ml cold homogenizing buffer (0.075 M NaCl, 0.024 M Na_2EDTA, pH 7.5) using bench top homogenizer (PRO Scientific, USA) centrifugation at 1500 rpm for 10 minutes. 75 µL of nuclear suspension (supernatant) was mixed with 75 µL of 2% low melting (LGT) agarose (Nacalai Tesqe, Inc. Kyoto, Japan) at 45°C and the mixture was layered on the fully frosted slide using a cover slide. Finally, 100 µl of normal agarose 1% was rapidly layered on the surface and covered with another slide and allowed to gel. Slides were placed in a chilled lysing solution (2.5 M NaCl, 100 mM Na EDTA, 10 mM Tris buffer, 1% sarkosyl, 10% DMSO, and 1% Triton X-100, pH 10) and kept at 0°C in the dark for 60 min, then in chilled alkaline solution (300 mM NaOH and 1 mM Na EDTA, pH 13) for 10 min in the dark. Electrophoresis was conducted for 15 min at 25 V and approximately 300 mA. The slides were neutralized for 7 minutes and dehydrated in ethyl alcohol for 5 min. Dried at room temperature, stained with 50 µl of (20 µg/ml) ethidium bromide. Slide were examined by fluorescence microscope (Olympus BX-43, Japan) equipped with a green filter, 50 nuclei per slide were analyzed using Comet Assay Software Project (CASP) to measure different comet parameters and to obtain DNA migration.

STATISTICAL ANALYSIS

Statistical analyses were conducted using SPSS software package version 16.0. Data were analyzed using one-way analysis of variance (ANOVA) followed by Lowest significant difference (LSD)

multiple range test. All data were expressed as mean ± SE for all experimental and control animals. P < 0.05 was considered significant compared to control.

RESULTS

Acute exposure of rats to 26 mg/kg b.w. of lambda cyhalothrin for 24 hours caused hind limb abnormality appeared as splayed gait for half the number of animals (Fig.1), these animals died within few hours after the second dose while the rest of this group showed the same signs and still alive.

Lipid peroxidation (MDA) and antioxidant status (GPx) in serum

Table 1 shows that acute exposure to LCT caused significant increase of serum MDA level at 24 (P< 0.05) and 48 hours (P<0.01) in comparison with control. On the other hand serum GPx level significantly decreased at 24 and 48 hours (P<0.01).

DNA damage in brain tissue

Comet assay parameters indicated that exposure of rats to LCT for 24 hrs caused increased tail length P<0.05) while 48 hours exposure induced severe DNA damage indicated by increased DNA % in tail, tail length and tail moment (Table 2 & fig. 3). Fig. 2 shows the shape of comet head and tail by comet assay.

DNA damage in liver tissue

LCT induced hepatic DNA damage at 24 and 48 hours expressed in all comet parameters. DNA % in head was decreased while % of DNA in tail, tail length and tail moment were significantly decreased in comparison with control. (Table 3 & Fig. 4).

Histopathology of brain tissue

Cerebrum of rats exposed to LCT for 24 hrs. showed sub meningeal perivascular hemorrhage in some areas accompanied with thrombosis of blood vessels, decrease in the thickness of the pyramidal layer of hippocampus and severe damage of neurocytes in the form of pyknotic, shrunken and hyperchromatic nuclei of hippocampal neurons (Fig. 5A). While 48 hrs. Exposure caused demyelination of neurons (Fig. 5B). On the other hand cerebellum of exposed rats showed severe pycknotic degeneration of purkinje cells associated with vacuolation along its monolayer accompanied with hemorrhage in the cerebellar medulla (Fig. 5C). These changes accompanied with slight increase in number of Bergmann astrocyte cells, which increased in its severity after 48 hrs. The purkinje cells dissociated and showed slight disorganization of purkinje cells with karyolysis of its nucleus (Fig. 5D).

Histopathology of liver tissue

Fig. 6 shows hepatic changes induced by LCT at 24 hrs as congestion of blood vessels and proliferation of kuppfur cells while 48hrs exposure showed congestion of blood vessels and slight vacuolar degeneration of hepatocytes.

Table 1: **MDA (nmol/ml) and GPx (U/l) levels in serum of rats exposed to LCT in comparison with control**

	MDA(nmol/ml)		GPx(U/l)	
	Control	LCT	Control	LCT
24hrs	5.36 ± 0.97	7.95 ± 1.88*	89.82 ± 3.22	52.85 ± 3.54**
48hrs	5.29 ± 1.37	10.26 ± 0.01**	89.30 ± 2.78	38.37 ± 0.75**

Data are expressed as means ± S.D.*denotes P < 0.05 and ** denotes P < 0.01 as compared with control group.

Table 2: **Head DNA % and Tail DNA% in brain at 24 and 48 hours exposure to lambda cyhalothrin in comparison with control.**

	Brain DNA damage at 24 Hrs.		Brain DNA damage at 48 Hrs	
Group	Control	LCT	Control	LCT
Head DNA %	95.85 ± 0.42	93.07 ± 0.97	96.51 ± 0.44	80.01 ± 2.42**
Tail DNA %	4.15 ± 0.42	6.93 ± 0.97	3.49 ± 0.44	19.99 ± 2.42**

Data are expressed as means ± S.E. ** P < 0.01 means highly significant difference when compared with control group.

Table 3: **Head DNA % and Tail DNA% in liver at 24 and 48 hours exposure to lambda cyhalothrin in comparison with control.**

	Liver DNA damage at 24 Hrs.		liver DNA damage at 48 Hrs	
Group	Control	LCT	Control	LCT
Head DNA %	97.86±0.60	92.33 ± 1.38**	98.36±0.59	86.46± 1.24**
Tail DNA %	2.14±0.60	7.67± 1.38**	1.64± 0.59	13.54±1.24**

Data are expressed as means ± S.E. ** denotes P < 0.01 as compared with control group.

Fig. 1: **A rat exposed to 26 mg/kg body weight of LCT showing tip toe and splayed gait of the hind limbs.**

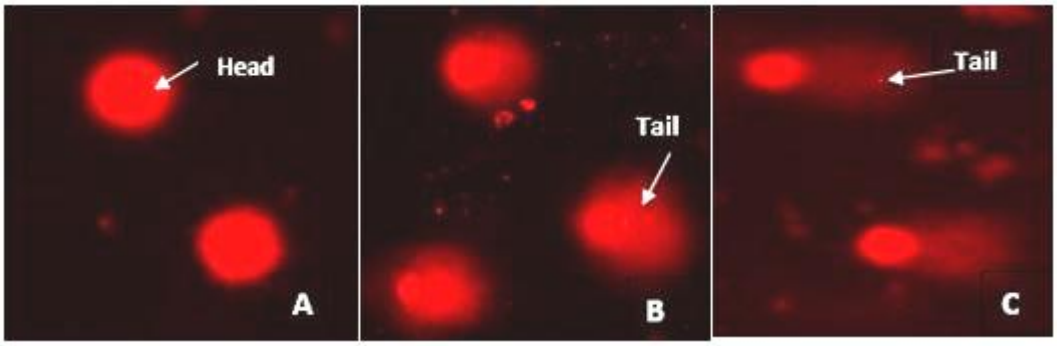

Fig. 2: **Comet assay showing DNA damage; A undamaged DNA, B and C are damaged DNA appear as long tail.**

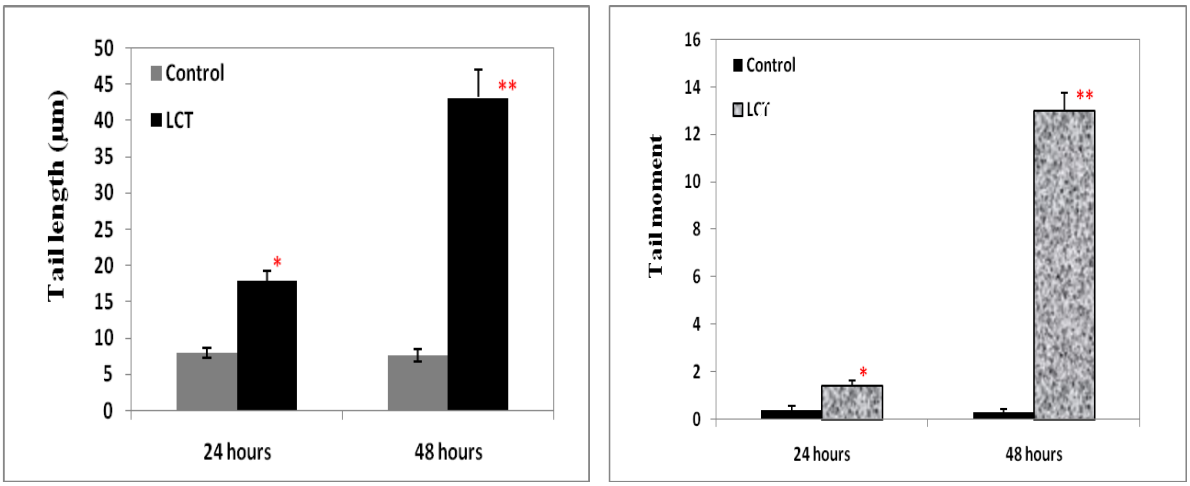

Fig. 3: Tail length and tail moment in brain tissue at 24 and 48 hours.

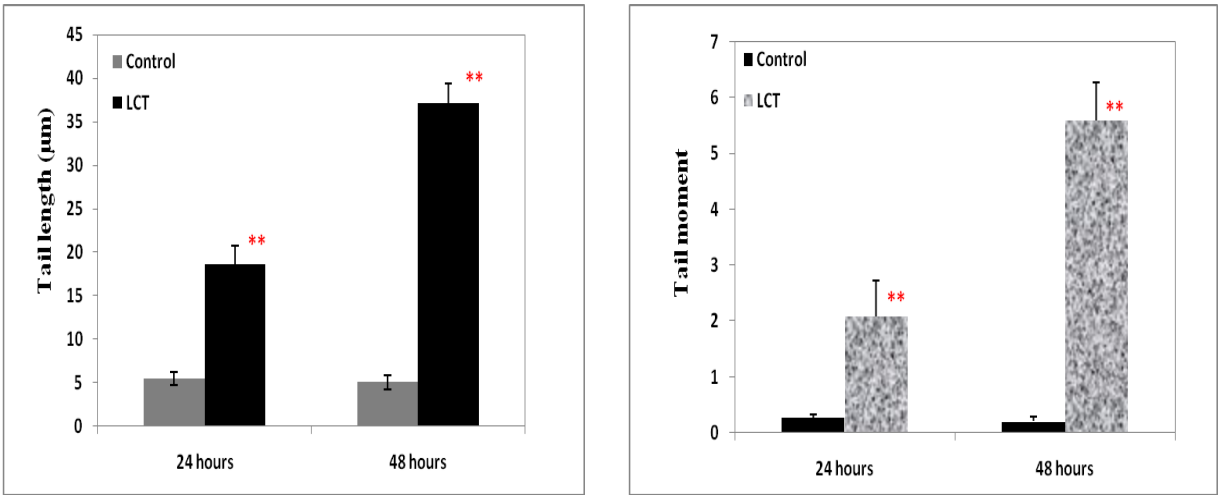

Fig. 4: Tail length and tail moment in liver tissue at 24 and 48 hours.

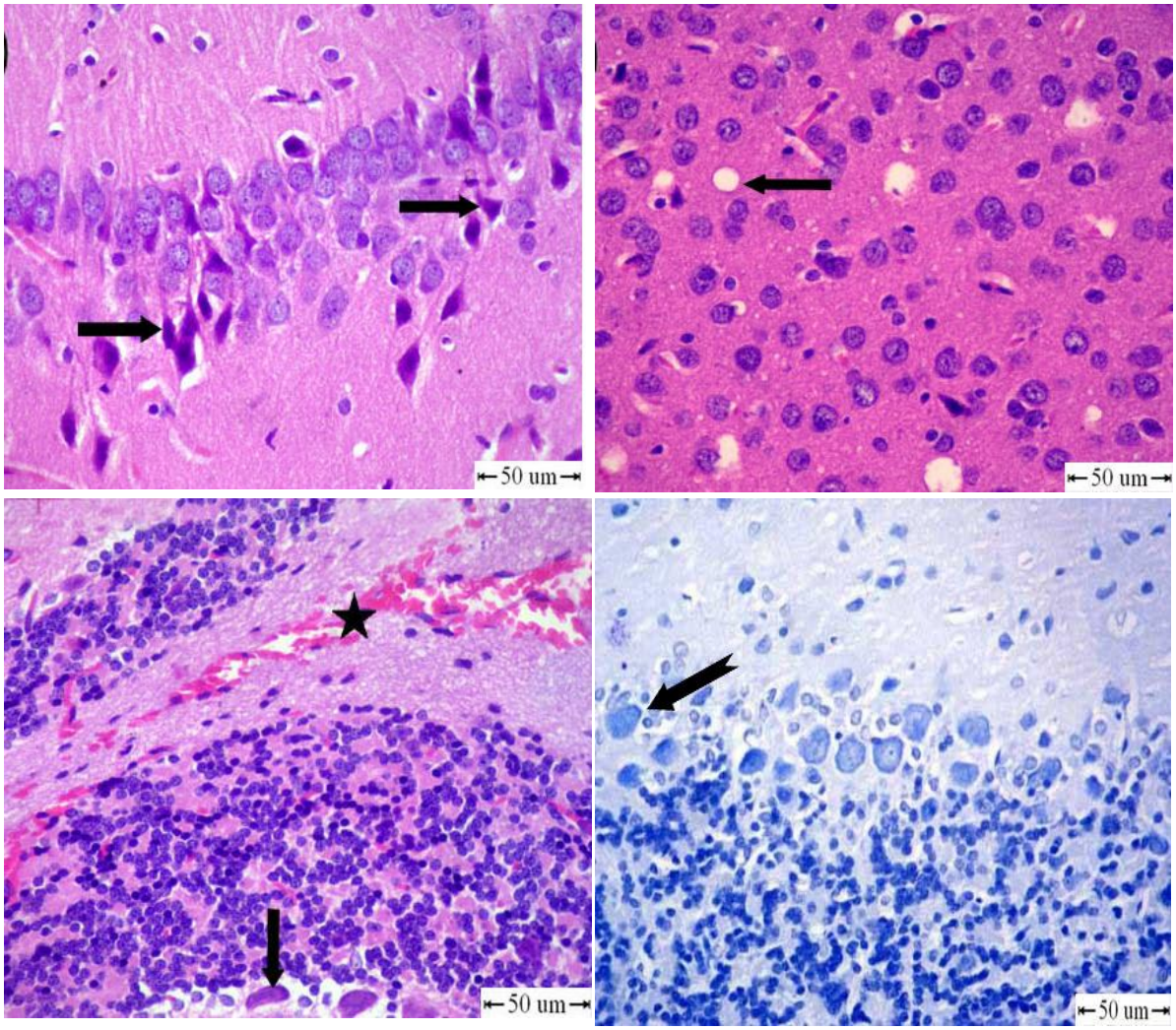

Fig.5: A: Cerebrum of rats exposed to LCT for 24hrs showing pyknotic degeneration of hippocampal neurons (arrow). (B): 48hrs showing demyelination (arrow), (H&E, bar= 50 um). C: cerebellum of rats exposed to LCT for 24 hrs. showing pyknotic degeneration of purkinje cells (arrow), hemorrhage in medulla (star). (D): 48hrs showing dissociation of purkinje cells with karyolysis of its nucleus (notched arrow) (Toluidine blue).

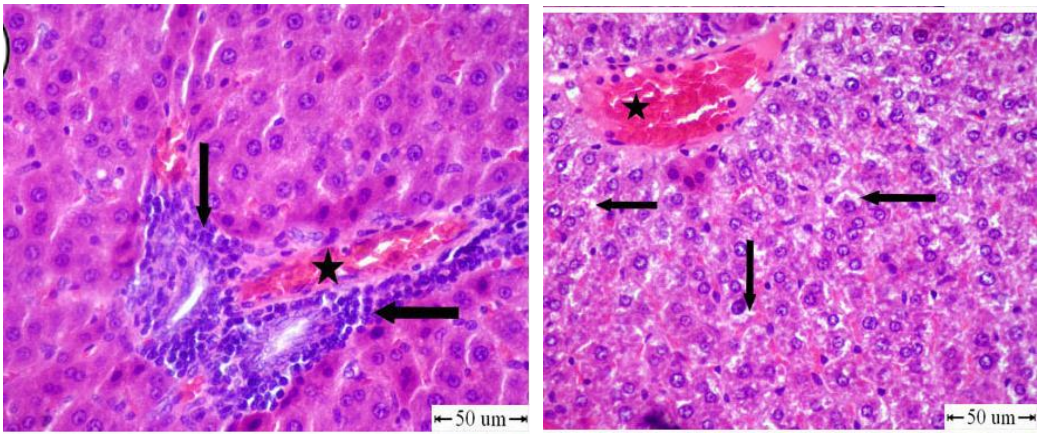

Fig. 6: A: liver of rat exposed to LCT 24 hrs showing congestion of blood vessels (star) and proliferation of kuppfur cells (arrow). B: LCT group after 48 hrs showing congestion of blood vessels (star) and slight vacuolar degeneration of hepatocytes (arrow), (H&E, bar= 50 um).

DISCUSSION

Synthetic pyrethroids are neurotoxic insecticides, the present study revealed sings of neurotoxicity appeared as splayed gait and backward stretching of the hind limb at 24 and 48 hours exposure. Ray & Fry (2006) reported that pyrethroids induce their neurotoxic effects through voltage-dependent sodium channels. LCT delays the closure of sodium channels leads to accumulation of sodium inside the cells and increases cell membrane excitability, the extended opening of sodium channels lowers the threshold of sensory nerve fibers for the activation of further action potentials, resulting in repetitive firing of sensory nerve endings (Vijverberg & van den Bercken, 1990) that may progress to hyperexcitability of the entire nervous system (Narahashi *et al.*, 1995).

Histological changes in brain of exposed rats may explain the cause of these clinical signs as the cerebrum showed sub meningeal hemorrhage and thrombosis of blood vessels, accompanied with severe damage of neurocytes in the form of pyknotic, shrunken and hyperchromatic nuclei of hippocampal neurons and demyelination of neurons in addition to cerebellar changes that appeared as severe pycknotic degeneration of purkinje cells associated with hemorrhage in the cerebellar medulla. These changes accompanied with slight increase in number of Bergmann astrocyte cells, which increased in its severity after 48 hrs. The purkinje cells dissociated and showed slight disorganization of purkinje cells with karyolysis of its nucleus. These results are similar to a study on animals exposed to lambda cyhalothrin insecticide that induced noticeable significant changes in brain (Abdel- Mobdy & Abdel-Rahim, 2015).

Oxidative stress induction is one of the main mechanisms of action of many pesticides; it involves an excessive production of reactive oxygen species (ROS) or oxygen free radicals resulting from impaired balance between the ROS generation and antioxidant defense capability (Abdollahi *et al.*, 2004; Amin & Hashem, 2012). In the current study, LCT induced oxidative stress represented as increased MDA ($P< 0.05$) level and decreased GPx ($P<0.01$) these data support that of previous studies which suggest the involvement of oxygen free radicals in the toxicity of pesticides (Bagchi *et al.*, 2002, Lee *et al.*, 2017). WHO (1990) reported that toxicity of LTC might be due to the release of cyanohydrins, which are unstable under physiological conditions and further decay to cyanides and aldehydes, which act as a source of free radicals.

Production of oxidative stress and free radicals caused by insecticides can produce DNA damage (Needham *et al*., 2007; Bertram & Hass 2008; Heikal *et al*., 2012). In the present study comet assay could detect DNA damage in brain and liver of LCT exposed groups; comet assay parameters such as % of DNA in head, % of DNA in tail and tail length are used to indicate that there is some degree of DNA damage and exposure to a genotoxic substance while tail moment express the severity of DNA damage (Knopper *et al*., 2005) because it is calculated as % DNA in tail X tail length (Tice *et al*., 2000) so it is more accurate indicator. The present data showed that LCT induced extensive DNA damage in brain and liver at 24 and 48 hours and all parameters were significantly changed from control group except brain tissue at 24 hours the % of DNA in head and tail did not change but tail length and tail moment were significantly increased ($P<0.05$). DNA damage induced by LCT in brain and liver was in relation with oxidative stress these results could confirm the role of oxidative stress in DNA damage.

Insecticides are known to induce various histological changes in liver tissues (Elsharkawy *et al*., 2013; Ezzi *et al*., 2016). LCT acts as several other insecticides and adversely affects on the cytochrome P450 system or the mitochondrial membrane transport system of hepatocytes (Gokcimen *et al*., 2007). The current study showed that LCT caused congestion of hepatic blood vessels, proliferation of kuppfur cells and vacuolar degeneration of hepatocytes. These data agree with Lakkawar *et al*. (2004) and Singh *et al*. (2015). The present study concluded that acute exposure to LCT caused neurotoxic signs, oxidative stress and DNA damage in brain and liver that was detected by comet assay.

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تكسير الحامض النووي و تغيرات باثولوجيه في مخ وكبد فئران سبراغ دولي بالمبيد الحشري لمبدا سيهالوثرين

ضحي يحيي ، مروه فاروق علي

الملخص :

مركب اللمبدا سيهالوثرين هوعباره عن مبيد حشري بيرثرويدي يستخدم في جميع انحاء العالم وقد هدفت هذه الدراسه الي معرفه مدي تاثير هذا المركب علي تكسير الحامض النووي في المخ والكبد وعلاقته بضغوط الاكسده في ذكور الفئران البيضاء البالغه، هذا بالاضافه الي التغيرات االباثولوجيه. تم تجريع الفئران بثلث الجرعه المتوسطه المميته من ماده اللمبدا سيهالوثرين المذابه في زيت الذره لمده ٢٤ ساعه ، و ٤٨ ساعه وتعرضت المجموعه القياسيه للمذيب فقط. تم تخدير الحيوانات وتجميع عينات الدم من الوريد بدون مضاد للتجلط للحصول علي مصل الدم ، كذلك تم اخذ المخ والكبد وتجزئته بحيث استخدم جزء لتحليل درجه تكسير الحامض النووي والجزء الاخر تم تثبيته بمحلول الفورمالين للفحص النسيجي. اكدت النتائج ان التعرض الحاد لهذا المبيد ادي الي حدوث ضغوط اكسده الي جانب تكسير شديد في الحامض النووي مع حدوث تغيرات باثولوجيه في انسجه المخ والكبد للفئران المعرضه وذلك مقارنه بالمجموعه القياسيه.

خلصت النتائج الي ان مبيد اللمبدا البيرثرويدي له تاثيرسام للجينات في المخ والكبد مع التاكيد علي أهميه استخدام تحليل الكوميت للحامض النووي وهو اختبار حساس ودقيق لتحديد السميه الجينيه الناتجه عن التعرض للمبيدات.