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TAURINE MODULATES NEUROBEHAVIORAL IMPAIRMENTS IN LAMBDA CYHALOTHRIN INDUCED MALE ALBINO RATS

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ABSTRACT

Taurine, a sulfur-containing α-amino acid, is widely distributed in most mammalian tissue. Lambda cyhalothrin (LCT), is a broad-spectrum type II synthetic pyrethroid that imitate the properties of the natural insecticide pyrethrin from chrysanthemum flowers. The aim of this study was to evaluate the modulatory role of taurine (TAU) on locomotor activity and neurobehavioural alterations in LCT intoxicated male albino rat. Mature 36 Wistar male albino rats were randomly divided into six groups. After pre-treatment of taurine (50 mg/kg body weight), lambda-cyhalothrin was given orally for consecutive 14 days at two dose levels (10.83 and 15.17 mg/kg body weight) alone or in combination. Neuro-behavioural changes or signs of intoxications were measured by behavioural studies including locomotor and non-locomotor activities (Open-field test) and mouse-killing (muricide)

test. Brain serotonin level was evaluated spectrophotometrically from control and treated rat brain tissue. In LCT treated rats, a significant decrease in locomotor activity, emotional behavior and cerebral and cerebellar serotonin level were seen. Exposure to LCT thus elicited significant changes in neurobehavioral activity and emotional behaviour and significant restoration were observed due to pre-administration of taurine. In conclusion, these results indicate that the ability of TAU as a neuromodulator to protect brain against LCT-induced neurobehavioral alterations.

KEYWORDS: Taurine; Lambda cyhalothrin; Neurohavioural activity; Emotional behaviour; Serotonin level.

INTRODUCTION

Brain is the most vital organ in the animals which control and coordinate other vital organs and their physiological functions. In active and steady state of the animal, the brain is always active; however, its functioning can be influenced by the effects of xenobiotics.^[1]

Pesticides exert harmful effects on many non-target organisms including humans. In whole world, more than 30% used pesticides in the agricultural fields as well as in other application sectors, are synthetic pyrethroids.^[2] It is reported that pyrethroids affect the behaviour of adult mammals by interfering with the nerves and brain functioning.^[3] High doses of pyrethroids can cause numbness, itching, burning, stinging, tingling, or warmth that may last for few hours.^[4] They are also acknowledged to cause dizziness, headache, nausea, muscle twitching, reduced energy, convulsions and loss of consciousness that could last for several days. Recently, many studies have reported that exposure to pesticides in humans may be the reason for mild to severe neuro-physiological and neurobehavioral abnormalities.

Lambda cyhalothrin (LCT), a synthetic type II Pyrethroid, is a replacement of cyhalothrin, is the active ingredient in several commercial pesticide products ^[5] and is an enriched isomeric form of the two biologically active stereoisomeric pairs of cyhalothrin isomers. ^[6] LCT is a non-systemic broad spectrum insecticide used to protect crops from aphid, beetle and caterpillar pests as well as most against cockroaches, mosquitoes and flies responsible for disrupting the public health in non-agricultural fields. Ansari et al., (2012), ^[7] reported that neurobehavioral changes may be more prominent after exposure to LTC. LCT generates neurotoxicity primarily interfering in voltage-gated sodium channel and also disrupts calcium and chloride channels in the CNS. ^[8,9] Due to their lipophilic nature, pyrethroids effortlessly enter into biological cell membranes and LCT penetrates the insect cuticle in rapid manner and interrupts nerve conduction within few minutes leading to cessation of feeding, loss of neuro-muscular control, paralysis, and ultimately leads to death. ^[10,11]

It is well acknowledged that serotoninergic neurons situated in the medulla, are capable to initiate locomotor activity. This effect is exercised by actions on motoneurons and on neurons of the locomotor CPG (Central Pattern Generator).^[12] Motoneuron and interneuron excitability is augmented, and putative CPG interneurons display oscillatory behaviour in

response to serotonin receptor stimulation. The medullary serotonergic nuclei show multiple roles in the regulation of locomotion.^[13]

In response to the testing conditions, the summation of movements in any part of the body regardless of the distance moved in horizontal or vertical direction is considered as motor activity. Motor activity comprises of locomotor and non-locomotor movements. Locomotor activity denotes ambulation, i.e. an alteration in the coordinate position of the subject within the testing device by walking, running, circling, or rearing. Scratching, pawing, grooming, burrowing, head or body shakes, and sniffing are designated as non-locomotor activity. The result of the interactions between the test subject and the testing apparatus gives the quantitative measurements of motor activity. These interactions are noted as patterns of motor-activity measurements that match up to complex behaviours presented by the experimental animal throughout the testing trial and this is done in response to a new environment. These consist of motivation, exploration, habituation, anxiety, and fear. [14,15] A test chemical may efficiently modify these interactions, which leads to alterations in the pattern of motor activity witnessed during the testing phase. Thus, motor-activity measurements represent a "composite score" that may encompass alterations in a number of distinctive behaviours rather than a change in a single and definite behaviour. [16] The output of interaction and coordination of central nervous system (CNS) and peripheral nervous system (PNS) is expressed in animal behaviour. To assess locomotor activity and neurobehavioural changes in animals, a battery of tests is needed.

Taurine (TAU) or 2-amino ethane sulfonic acid, is mostly distributed in high concentrations in animal brain, liver, kidney, heart, lens, and reproductive organs.^[17] In these tissues, TAU acts as a neurotransmitter, ^[18] cell volume regulator, antioxidant, growth promoting factor and exhibits a neuroprotector activity. TAU was found to have a modulated action against neurotoxicity.^[19] TAU induces hyperpolarisation and inhibits firing of central neurons.^[20]

Therefore, the current study was aimed to investigate the modulatory role of taurine (TAU) on locomotor and non-locomotor activities as well as on neurobehavioural alterations in LCT intoxicated (at two different dose levels) male albino rat.

MATERIALS AND METHODS

LCT 5% Emulsifiable Concentrate (EC) was purchased from RPC Agro Industries, Kolkata. Two respective doses 10.83(1/7th LD50 dose) and 15.17(1/5th LD50 dose) mg/kg body wt.

of LCT were applied.^[21] The selective dose of 50mg/kg body wt. of taurine were applied as an antidote. ^[21] TAU was purchased from Sigma-Aldrich, USA and other chemicals used were of analytical grade.

Animal care

Mature 36 Wistar male albino rats weighing between 130±15g were used for this experiment. The animals were housed in polycarbonate cages with sawdust bedding and was acclimatized for 10 days before start of the treatments at suitable temperature of 25°±2°C with 12 hrs light-dark cycle. Animals were supplied with standard laboratory feed and adequate water throughout the period of experimentation. Institutional Animal Ethics Committee approved the experimental protocol of this study.

Treatment protocol

Rats were randomly divided into six groups, and each group contains six animals. The experimental six groups were designed as

Group-I for **DW-Control** (Distilled Water, 2 ml/kg body wt.)

Group-II for **TAU-Control** (TAU, 50 mg/kg body wt.)

Group-III for **LCT-Low** (LCT, 10.83 mg/kg body wt.)

Group -IV for **TAU** + **LCT-Low** (TAU, 50 mg/kg body wt. + LCT, 10.83 mg/kg body wt.)

Group -V for **LCT-High** (LCT, 15.17 mg/kg body wt.)

Group -VI for **TAU** + **LCT-High** (TAU, 50 mg/kg body wt. + LCT, 15.17 mg/kg body wt.)

After one hour of the treatment of TAU (50mg/kg body wt), LCT was administered at two dose levels (10.83 and 15.17mg /kg body wt.) for consecutive 14 days. All animals were observed at least once daily to notice behavioural changes or signs of intoxications. Animal's weight was taken daily and the dose was adjusted accordingly to body weight.

Behavioural studies

Locomotor and non-locomotor activity by Open-field test

The open field study was carried out after modification of this method according to the method of Brown et al., $(1999)^{[22]}$ and Bikomo et al., $(2017)^{[23]}$ The open field apparatus was made up of white plywood and area of 72 x 72 cm was surrounded by 40 cm walls in height and within this area behavioural activity was measured. Out of four one wall was made by clear Plexiglass so that rats could be visible from the outside. The floor were divided into sixteen 18 x 18 cm square box by the use of blue marker pen and central 18x18 cm box were

drawn in the middle of the open field area by red marker pen. These blue lines are used to assess locomotor activity. The central square was used to measure high locomotor activity of rat that cross the lines of the test chamber many times during a test session. Also, the central square has sufficient space surrounding it to designate the central location as being distinct from the outer locations.^[24] All animals testing are conducted under diffuse lighting conditions with the help of a 60-Watt white light bulb. Rats were carried to the test room in their home cages and tested on one rat at a time. All experimental rats were handled by the base of their tails at all times. From their home cage, each rat were placed randomly into one of the four corners of the open field. They were allowed to explore the apparatus for 5-min while taking scores of their behaviour. After the 5-min test duration, the rats were scooped up from the open field and were kept to their home cages. The open field was cleaned with 70% ethyl alcohol and permitted to be dried between trials.

The following behaviors were examined by Open-field test.

- 1. *Locomotion* (Number of grid line crossing) is the frequency with which the experimental rat crossed one of the grid line with all four paws in the open field.
- 2. Rearing frequency is that with which the rat stands on hind legs or leans against walls of the box with front paws.
- 3. *Centre square entries* is the frequency with which the rat crossed one of the red lines with all four paws into the central square.
- 4. Latency was measured usually by time taken to leave start area in the open field.
- 5. Forepaw vibration, paw licking, washing of nose, face and head, body licking, genital grooming, scratching, and head-shaking were considered as *grooming behaviours*.
- 6. The frequency of *urination* was measured by the number of puddles or streaks of urine deposited on the floor of open field.
- 7. Defection was measured by counting the fecal boles deposited on the open field floor.

Mouse-killing (muricide) behavioural test

Mouse-killing is a normal activity of about 90% of wild rats and 10% of domestic rats and according to Karli et al. (1969),^[25] it is a strong instinctual and motivated behavioural process with a specific neurophysiological mechanism influenced by environmental and genetic factors. Horovitz et al (1965),^[26] first coined the term 'muricide' for mouse-killing behaviour and a standard pharmacological testing procedure 'muricide test' was developed for quantifying inhibition of mouse-killing by rats.^[27] The significance of mouse killing as a form

of predatory aggression has been firmly established since the initial observations by Karli (1956), [28] and later by the behavioral criteria used to define predatory aggression in the rat. [29] The muricidal test was carried out in the present study according to the method of Karli et al 1969. Rats of all experimental groups were isolated in individual cage before 7 days of muricidal test. A mouse were placed in a rat's home cage and mouse killing response were recorded within 5 min. If mouse killing were occurred before 5 min then killed mouse were removed within 20 to 50 sec from the cage in order to prevent the rats from eating them and this rat were considered as killer rat. In case of no killing response, the mouse were removed from the cage after 5 minutes. Lambda cyhalothrin (LCT) were applied at two different dose levels of 10.83 and 15.38 mg/kg body wt with pretreated taurine at 50 mg/kg body wt for consecutive 14 days to the rats before the muricide test. Mouse were placed in a rat's home cage, after 120 min of oral administration of LCT and taurine.

Determination of brain serotonin (5-HT)

Firstly, 0.25 ml of O-phthaldialdehyde (OPT) reagent was added to the homogenate. The fluorophore was developed by heating at 100°C for 10 min. The readings were taken at 360-470 nm in the spectrofluorimeter. For serotonin tissue blank, 0.25 ml of HCl without OPT was added. [30]

Statistical analysis

The data of behavioral and biochemical estimations were statistically analyzed by One-Way Analysis of Variance (ANOVA) followed by two-tail t-test using the Origin 6.0 Scientific data analysis and graphing software origin lab corporation (formerly Microcal Software, Inc.). The results were expressed as the Mean \pm Standard error of mean (SEM). The difference between group means was considered significant when p<0.05.

RESULTS

Effect on locomotion

The locomotion of rats of LCT treated low and high dose group were significantly reduced (p<0.001) compared to that of control group rat. However, pre-treatment of taurine before LCT treatment resulted in a significant increase in the locomotion in LCT treated rats of both groups as presented in figure 1.

Effect on latency behaviour

Latency behaviour of rat of LCT treated low and high dose groups were significantly increased (p<0.001) in comparison to that of control group rat. Pre-treatment of taurine before LCT treatment resulted in a significant decrease in the latency behaviour of both LCT treated rats (Figure 2).

Alteration in rearing behaviour

As shown in figure 3, the rearing behaviour of rats of LCT treated low and high dose groups was decreased significantly (p<0.001) than that of the control animals. However, the rearing behaviour was significant increased (p p<0.01) by taurine pre-treatment in both LCT low and high dose treated groups rats.

Effect on central square entry

The frequency of central square entry of rats of LCT treated low (p<0.05) and high dose (p<0.01) groups were decreased significantly than that of control rats. Taurine preadministration resulted in enhanced central square entry in LCT low and high dose treated group animals (Figure 4).

Grooming behaviour

As shown in Figure 5 the grooming activity of LCT treated low (p<0.01) and high dose (p<0.001) animals was decreased significantly than that of the control animals. However, the grooming activity was increased (p<0.05) by taurine pre-treatment in both low and high doses LCT treated rats.

Emotional behaviour

The frequency of urination (Figure 6) and counting the fecal boles (Figure 7) deposited on the floor were increased significantly and in LCT low and high dose treated animals in dose-dependent manner in comparison to that of control animals. Taurine pre-administration caused significant decrease in frequency of urination and fecal bole count in LCT low and high dose treated group animals.

Muricidal response

The muricidal activity of rats of LCT low and high dose treated groups were increased 16.66% and 33.33% respectively than that of control rats. Muricidal activity in LCT low and high dose treated group animals restored like normal control animals after taurine preadministration (Table 1).

Rat cerebral and cerebellar serotonin level

The cerebral and cerebellar tissue serotonin level of LCT treated low and high dose group rats were significantly reduced (p<0.001) compared to control group rats. However, pretreatment of taurine in LCT low and high dose treated animals resulted in a significant enhancement (p<0.05) in serotonin level (Figure 8, 9).

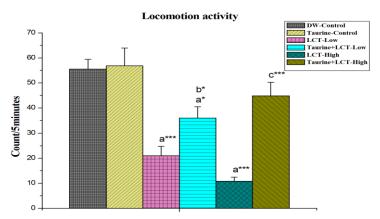


Figure 1: Effect of taurine on the locomotion of LCT exposed male albino rat. Results are expressed as Mean±SEM (N=6). Statistical analysis is done by ANOVA test followed by multiple comparison two-tail t-tests. Probability values with different superscripts (a, b, c) differ from each other significantly. Superscript a: Group-I VS all other groups; Superscript b: Group-III VS Group-IV; Superscript c: Group-V VS Group-VI. Asterisks represents the different level of significance (* indicates p<0.05, ***indicates p<0.001).

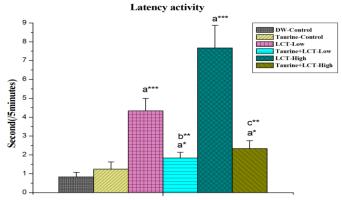


Figure 2: Shows the effect of taurine on the latency period of LCT exposed male albino rat. Results are expressed as Mean±SEM (N=6). Statistical analysis is done by ANOVA test followed by multiple comparison two-tail t-tests. Superscript a: Group-I VS all other groups; Superscript b: Group-III VS Group-IV; Superscript c: Group-V VS Group-VI. Asterisks represents the different level of significance (* indicates p<0.05, **indicates p<0.01,*** indicates p<0.001).

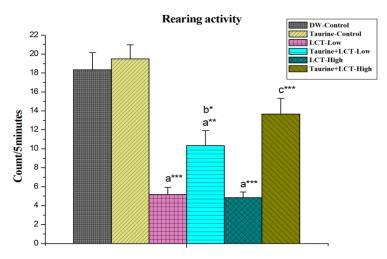


Figure 3: Effect of taurine on rearing behaviour of LCT exposed male albino rat. Results are expressed as Mean±SEM (N=6). Statistical analysis is done by ANOVA test followed by multiple comparison two-tail t-tests. Probability values with different superscripts (a, b, c) differ from each other significantly. Superscript a: Group-I VS all other groups; Superscript b: Group-III VS Group-IV; Superscript c: Group-V VS Group-VI. Asterisks represents the different level of significance (* indicates p<0.05, **indicates p<0.01,*** indicates p<0.001).

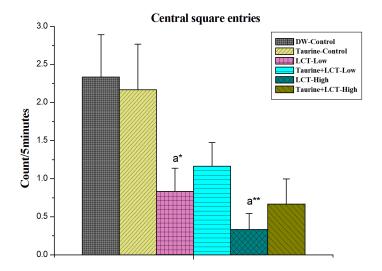


Figure 4: Shows the effect of taurine on the frequency of central square entries in lambda cyhalothrin exposed male albino rat. Results are expressed as Mean±SEM (N=6). Statistical analysis is done by ANOVA test followed by multiple comparison two-tail t-tests. Probability values with different superscripts (a, b, c) differ from each other significantly. Superscript a: Group-I VS all other groups. Asterisks represents the different level of significance (*indicates p<0.05, **indicates p<0.01).

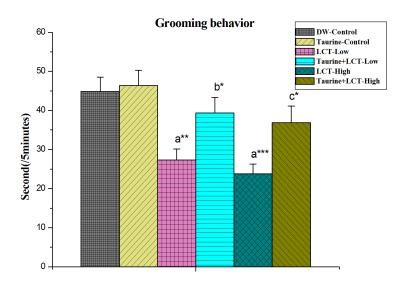


Figure 5: Effect of taurine on grooming activity in lambda cyhalothrin exposed male albino rat. Results are expressed as Mean±SEM (N=6). Statistical analysis is done by ANOVA test followed by multiple comparison two-tail t-tests. Superscript a: Group-IVS all other groups; Superscript b: Group-III VS Group-IV; Superscript c: Group-V VS Group-VI. Asterisks represents the different level of significance (*indicates p<0.05,**indicates p<0.01,*** indicates p<0.001).

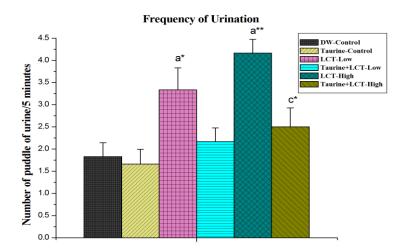


Figure 6 Shows the effect of taurine on urination in lambda cyhalothrin exposed male albino rat. Results are expressed as Mean±SEM (N=6). Statistical analysis is done by ANOVA test followed by multiple comparison two-tail t-tests. Superscript a: Group-I VS all other groups; Superscript c: Group-V VS Group-VI. Asterisks represents the different level of significance (*indicates p<0.05,**indicates p<0.01).

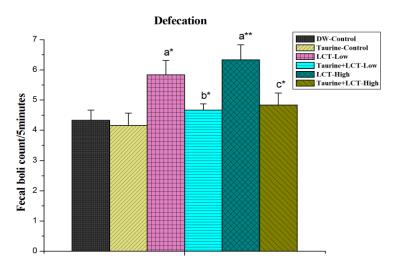


Figure 7: Effect of taurine on defecation in lambda cyhalothrin exposed male albino rat. Results are expressed as Mean \pm SEM (N=6). Statistical analysis is done by ANOVA test followed by multiple comparison two-tail t-tests. Probability values with different superscripts (a, b, c) differ from each other significantly. Superscript a: Group-I VS all other groups; Superscript b: Group-III VS Group-IV; Superscript c: Group-V VS Group-VI. Asterisks represents the different level of significance (* indicates p<0.05,**indicates p<0.01.

Table 1: Effect of taurine on LCT induced muricidal activity of male albino rats.

	Experimental Groups					
Muricidal Responses	Control (2 ml distilled	Taurine control (Taurine -	LCT low (LCT- 10.83	Taurine + LCT low (Taurine -50 mg/kg body wt. &	LCT high (LCT- 15.17	Taurine + LCT high Taurine (50 mg/kg body wt.)
	water/kg body wt.)	50 mg/kg body wt.)	mg/kg body wt.)	LCT-10.83 mg/kg body wt.)	mg/kg body wt.)	& LCT (15.17mg /kg body wt)
No. of Tested Rat	6	6	6	6	6	6
No. of Killers	0	0	01	0	02	00
% of Killers	0.000	0.000	16.666	0.000	33.333	0.000

The tabulated data represents the effect of taurine on the muricidal response in LCT exposed male albino rat. Results are expressed as percentage (N=6).

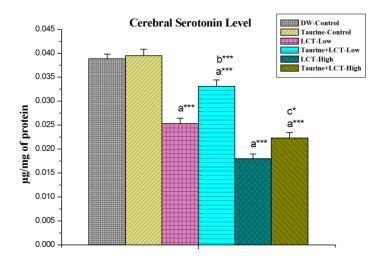


Figure 8: Shows the effect of taurine on cerebral serotonin level in LCT exposed male albino rat. Results are expressed as Mean±SEM (N=6). Statistical analysis is done by ANOVA test followed by multiple comparison two-tail t-tests. Probability values with different superscripts (a, b, c) differ from each other significantly. Superscript a: Group-I VS all other groups; Superscript b: Group-III VS Group-IV; Superscript c: Group-V VS Group-VI. Asterisks represents the different level of significance (* indicates p<0.05, *** indicates p<0.001).

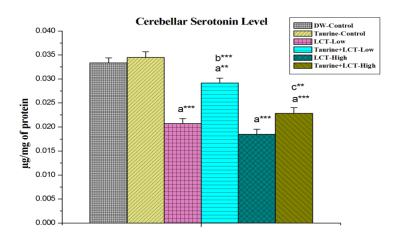


Figure 9: Effect of taurine on cerebellar serotonin level in LCT exposed male albino rat. Results are expressed as Mean±SEM (N=6). Statistical analysis is done by ANOVA test followed by multiple comparison two-tail t-tests. Probability values with different superscripts (a, b, c) differ from each other significantly. Superscript a: Group-I VS all other groups; Superscript b: Group-III VS Group-IV; Superscript c: Group-V VS Group-VI. Asterisks represents the different level of significance (**indicates p<0.01, *** indicates p<0.001).

DISCUSSION

In present study, the ameliorating effects of taurine on oral administration of Lambda cyhalothrin (LCT) induced locomotor and neuro-behaviour of rats was assessed. Locomotor and exploratory behaviour are usually tested for using Open field test. These behavioural tools simultaneously assess anxiety. [31] Behaviour such as frequency of line crosses, frequency of rearing, centre square entries, and latency and grooming are also used as measures of locomotion and neuro-behavioural activity. A high frequency of these parameters indicates increased locomotion and neuro-behavioural activity as well as reduced frequency of these parameters indicates its decreased state. The frequency of locomotion, rearing, centre square entries were and grooming significantly higher in the rats of control group compared to the LCT treated rats of both groups. On the other results were latency are increased in LCT treated rats than the control group rats. This present study is in agreement with a study similar to this where LCT caused reduced locomotion, [32] but there was no remedial measures but here taurine pre-treatment was able to restore these behavioural changes in LCT low and high dose treated animals in dose-dependent manner. It was reported that in the open field test, taurine modulated ethanol stimulated locomotor activity, [33] anxiolytic-like effects by increasing the number of central square entries, time spent in the central area and the anti-thigmotactic score while having no effect on the locomotor activity. [34] So taurine has the ability to retain the normal behavioural activity which are again seen in our study in LCT intoxicated rats.

The emotional condition of the experimental animals was judged by measuring the frequency of urination and counting the fecal boles deposited on the floor which increased significantly (Figure-6) in both LCT treated groups in dose-dependent manner as compared to control. However the emotional or anxiety behaviour was significantly restored (p<0.001) by taurine pre-treatment in both low and high doses LCT treated rats. Similar pattern of our findings was also observed by Rajawat et al. (2015)^[35] in cyfluthrin treated mice. In this regard GABAergic system has a vital role in the regulation of anxiety behaviour of animals. Taurine has the ability to interact with GABA receptors and thus the mimicing roles of GABA are seen.^[36]

Findings of the present study revealed that, pre-administration of taurine (50 mg/kg body wt.) produced a significant improvement of the altered behaviour induced by LCT. Taurine decreased the latency time in the open field test; however, ambulation, rearing and grooming

frequencies were insignificantly altered. Treatment with taurine restored the alterations accordingly and it might be suggested that 5-HT play a role in regulation of ambulation, rearing and grooming frequencies. Furthermore, these data corroborates previous investigations of Sayed et al. $(2012)^{[37]}$ and Tadros et al. (2005), where pre-treatment with taurine before the neurotoxin 3-nitropropionic acid (3-NP) injection significantly increased the locomotor activity of 3-NP-treated animals. Aragon et al. $(1992)^{[33]}$ also demonstrated that taurine-treated mice displays higher motor activity scores when the drug is given before alcohol.

Muricidal activity or Mouse-killing behaviour in the rat is one of most common predatory aggressive behaviours observed in the laboratory. [39,40,41] Growing evidence suggests that serotonin may play a central role in the regulation of muricidal activity, [42,43] although the neuronal circuitry involved in this behaviour is not clearly understood. In this study pretreatment of taurine after the oral administration of Lambda cyhalothrin (LCT) for consecutive 14 days showed ameliorative effects on muricide behaviour of rats. In present study, muricide behaviour was increased in LCT treated rats but pretreated taurine showed reverse response. There is many evidences to suggest strongly that central serotonergic systems may inhibit mouse killing behaviour in rats. This hypothesis is based on studies using 5-hydroxytryptophan (5-HTP) and para-chlorophenylalanine (PCPA). Injection of serotonin precursor, 5-HTP, caused reduction in the mouse killing behaviour due to increase in brain serotonine level but increase in mouse killing after PCPA injection was associated with a reliable reduction in brain serotonin and 5-hydroxyindoleacetic acid level. These results strengthen the hypothesis that brain serotonergic neurons are involved in inhibition of mouse killing behaviour. [44] In present study reliably suggests that intoxication of LCT cause increase in muricidal activity of rats in comparison to control animals and this may be due to the ability of LCT reduce the serotonin level in brain that is responsible for animal aggressive behaviour. On the other hand taurine inhibited the muricidal activity of rat by its neuroinhibitory effects in the olfactory bulb^[45] and that is documented by other study where 50% -100% of non-killing rats will killed mice after bulbectomy. [46] Mack et al., (1976). [47] have shown that mouse killing behaviour were inhibited when TAU injected in the olfactory blub of killer rats and also same results obtained when TAU was injected intraperitoneally. [47]

Interestingly, in our study, the cerebral and cerebellar tissue serotonin level of LCT treated low and high dose group rats were significantly reduced and pre-treatment of taurine in LCT

low and high dose treated animals resulted in a significant enhancement in serotonin level (Figure 8, 9). It is well known that serotoninergic neurons of medulla initiate locomotor activity and this effect is mediated through motoneurons and the locomotor CPG. [12] For the control of locomotion the medullary serotonergic nuclei play multiple roles. Activation of serotonergic receptors can re-establish locomotor movements. [13,48] Urszula Sławińska et al., 2014 reported that pharmacological treatment of a combination of 5-HT2 and 5-HT1A/7 agonists could persuade full weight-bearing locomotion in the upright posture. [49]

CONCLUSION

The results of the present study confirm that the exposure to LCT may lead to functional alterations associated with nervous system and taurine was able to reverse the neurobehavioral impairments induced by LCT by its neuromodulatory mechanism. Due to this taurine may be useful as a neuroprotective agent against LCT induced alterations in locomotor and neurobehavioural activity.

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