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λ-cyhalothrin induced sex-specific inflammation, glia activation and GABAergic interneuron disruption in the hippocampus of rats

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Abstract

Background Glia mediated neuroinflammation and degeneration of inhibitory GABAergic interneurons are some of the hall marks of pyrethroid neurotoxicity. Here we investigated the sex specific responses of inflammatory cytokines, microglia, astrocyte and parvalbumin positive inhibitory GABAergic interneurons to λ-cyhalothrin (LCT) exposures in rats.

Methods Equal numbers of male and female rats were given oral corn oil, 2 mg/kg.bw and 4 mg/kg.bw of LCT for fourteen days. They were euthanized on day 15, brains were excised and hippocampus ($n=5$/group) isolated for interleukin 1 beta (IL-1β) and tumor necrotic factor alpha (TNF-α) analysis. The remaining brains ($n=3$/group) were processed for Ionized calcium binding adaptor molecule 1 (Iba1), glial fibrillary acidic protein (GFAP) and parvalbumin (PV) distribution in the hippocampus. All quantitative data was subjected to one way analysis of variance (ANOVA).

Results LCT caused sex and dose dependent increase in IL-1β and TNF-α concentrations, distribution of microglia (Iba1+) and astrocytes (GFAP+), and reduction of PV + GABAergic interneurons. These effects were greater in males compared to females, and dose-dependent in both sexes.

Conclusion LCT specifically induced inflammation and disrupted GABAergic interneurons' integrities via activation of microglia and reactive astrogliosis and such effects are dose-dependent and sexually dimorphic.

Highlights

- Oral λ-cyhalothrin dose-dependently increases hippocampal inflammatory biomarkers, with more effects in male rats.
- Oral λ-cyhalothrin triggered microglia activation and reactive astrocytes in the hippocampus, with more effects in the males compared to the female.

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- λ-cyhalothrin exposure caused degenerative like pathologies in the PV+inhibitory GABAergic interneurons in the hippocampus.
- In general, more effects were observed in the male rats than the female, suggesting sex specificity in λ-cyhalothrin neurotoxicity.

Keywords Glia, Inflammation, GABA, λ-cyhalothrin, Hippocampus, Sex

Backgrounds

In an effort to increase agricultural gains by controlling vector attacks and control the spread of vector borne diseases, like malaria, pyrethroids constitute one of the mostly used insecticides worldwide [1, 2]. They are few of the perceived safer agents in household, agriculture and industrial control of health and economically affective insecticides. This perception led to the indiscriminate use of the agents, resulting in undesired health hazards in non-target organisms, including humans [3, 4], with evidences of oxidative damages, compromised antioxidant system and gut biome, DNA damage, cellular and organelle toxicity, apoptosis [3–5]. One of the most frequently used broad spectrum pyrethroids, λ-cyhalothrin, accesses the blood brain barrier (BBB) and causes neurotoxicity by prolonging the opening and delaying the closure of the sodium channels, leading to neuronal hyperexcitability.

λ-cyhalothrin (LCT) have been implicated to cause excessive salivation, cough, fatigue and pain [6], with modular activities on GABAergic and Dopaminergic neurotransmission in the central nervous systems [7], all enabled because of its potent accumulation in the brain. Immunotoxic responses, characterised by inflammation in different biological systems following exposures to LCT have also been reported in previous studies, including the immune defence of the nervous [8–10].

The resident immune cells of the nervous systems are microglia and astrocytes, whose activation signals neuroinflammation in many neurological insults and disorders, including pyrethroid neurotoxicity [11–13]. Microglia activation mediated inflammatory events are evidenced by the release of inflammatory cytokines [11, 14]. Also, synonymous to neurons is the microglial voltage gated sodium channels (VGSC), which mechanistically facilitate the direct activation of microglia by pyrethroid insecticides, a phenomenon that played out when microglia were exposed to permethrin and deltamethrin [15].

Due to the vulnerability of the sodium channels to LCT, and the resulting neuronal hyperexcitability, it was suspected to affect the efficiency of inhibitory gamma-amino butyric acid GABAergic interneurons in the brain [7]. Insecticides are reported to decrease hippocampal concentrations of GABA, GABA-producing enzyme glutamate decarboxylase 67 (GAD-67) [14] and GABAergic interneurons expressing the calcium binding protein parvalbumin (PV), the neuropeptide Y (NPY) and somatostatin (SS) [16, 17].

Understanding the social relevance of sex specific susceptibility to environmental neurotoxicity [18–22], thus, this study investigated the sex specific effects of LCT ingestions on inflammatory cytokines, microglia, astrocyte and parvalbumin positive inhibitory GABAergic interneurons in rats.

Methods

Ethical approval

This research was approved by the University of Ilorin ethical review committee (UERC) (UIL/UERC/11/46KA072), following the recommendation of the College of Health Sciences ethical review committee, in compliance with the Institutional Animal Care and Use Committee (IACUC).

Animals and experimental design

Forty-eight adult male and female Wistar rats with an average weight of 180 ± 200 g was obtained from the University of Ilorin Biological Garden, Ilorin. They were housed in cages and fed with standard laboratory diet and water *ad libitum*, in the animal holding unit of the Faculty of Basic Medical Sciences, College of Health Sciences, University of Ilorin, Ilorin. The rats were exposed to a 12 h light/dark cycle at room temperature for 7 days before the commencement of the experiments. All rats were handled in accordance with the standard guide for the care and use of laboratory animals.

Treatment plan

The animals were randomly divided into 3 groups of male ($n = 8$) and female ($n = 8$) rats as described below:

Control - received Corn oil (1 ml/kg.bw orally) daily
Low LCT - received oral ingestion of LCT 1/20 LD50 (2 mg/kg.bw) daily [23, 24]
High LCT – received oral ingestion of LCT 1/40 LD50 (4 mg/kg.bw) daily [23, 24]

Animals were treated for a period of fourteen (14) consecutive days.

Animal euthanasia

24 h after the last exposure, the rats were euthanized with intramuscular ketamine (10 mg/kg). The brains of rats designated for biochemical evaluations were removed and weighed. Hippocampal tissues (from Bregma

– 10 mm to – 15 mm) of five brains from each group was grossed out, dipped in 30% sucrose solution for further processing.

Animals designated for immunohistochemistry study were perfused transcardially with normal saline followed by 10% buffered formal saline. The brains were excised and stored in specimen bottles containing 10% buffered formal saline.

Biochemical evaluation

Hippocampal tissues were homogenized in 0.2 M cold sucrose and centrifuged at 2500 rpm for 10 min. The supernatant was then collected in tubes for Interleukin 1-Beta (IL-1β) and Tumour Necrosis Factor- alpha (TNF-α) analysis.

A high sensitivity and specificity Cusabio's enzyme-linked immunosorbent assay (ELISA) kit was used detect IL-1β, while Cusabio Rat TNF-α ELISA Kit (Catalog Number. CSB-E11987r) was used for quantitative analysis of TNF-α. In brief, 100 µl of standard or sample was incubated for 2 h at 37 °C, then 100 µl of Biotin-antibody (1x) was added for an hour incubation at 37 °C, followed by two washes. Next, the samples were incubated in 100 µl of horseradish peroxidase (HRP)-avidin (1x) for 1 h at 37 °C, followed by five washes, and a 15–30 min incubation in 90 µl of TMB substrate at 37 °C. Lastly, 50 µl of stop solution was added, mixed, and then the optical density was determined within 5 min, using a microplate reader set to 450 nm.

Ionized calcium binding adaptor molecule 1 (Iba1), glial fibrillary acidic protein (GFAP) and parvalbumin (PV) immunohistochemistry

To demonstrate the immunostaining of glia marker and inhibitory GABAergic interneurons in the hippocampal sections following exposures LCT, the remaining 3 rats from each group were perfused with 10% buffered formalin, their brains removed and processed for immunohistochemical staining with anti-Iba1, anti-GFAP and anti-PV in the hippocampus.

Paraffin embedded hippocampal tissues from each of the three brains per group were serially sectioned at 8 µm thickness, to achieve three sections for each stain, from each brain. The sections were deparaffinized with xylene, rehydrated through descending grades of ethanol (100%, 95%, 70% ethanol), and treated for protein un-masking in citrate-based solution (heat-mediated antigen retrieval), pH 6.0 (Vector®, Burlingame, CA, USA) for 30 min in a steamer. Sections were washed in PBS for 2 min, treated with 0.3% hydrogen peroxide solution in PBS for 10 min to achieve endogenous peroxidase blocking, washed again in PBS for 2 min and then incubated in 2.5% normal horse serum for 20 min for protein blocking. The sections were then incubated for 2 h at room temperature in primary antibodies: Goat polyclonal Iba-1 (Abcam, USA, ab5076) at 1:250, Mouse monoclonal GFAP-HRP conjugated (Santa Cruz, USA, 2E1: sc-33673) at 1:150 or Rabbit polyclonal PV antibody (Novus Biologicals, USA, NB120-11427) at 1:1000, followed by 5 min wash in PBS. Sections were incubated in ImmPRESS™ HRP Anti-Rabbit, Anti-Goat or Anti-Mouse IgG (Peroxidase) Polymer Reagent, raised in horse (Vector® Labs, USA), for 30 min. They were washed in PBS for 5 min twice, 3, 3 -diaminobenzidine (DAB) Peroxidase Substrate Kit (Vector® Labs, USA) was added to develop color, rinsed well in tap water, and then counter-stained in haematoxylin. Lastly, the ssections were dehydrated through ascending grades of ethanol (70%, 95%, 100%), cleared in Xylene, mount with Permount (Fischer Scientific, USA), and reaction sites were visualized as a brown staining.

Microscopy and Photomicrography

Microscopy and Photomicrography

Three hippocampal sections from each of the three brains prepared for histochemistry stains were finally examined under an AmScope 40X-2500X LED Lab Compound Microscope and photographed using the AmScope 5.0 MP USB Still Photo & Live Video Microscope Imager Digital Camera 5MP, manufactured by iSCOPE corp., USA. Approximately 165 randomly selected images (27 per group) were captured at 400X magnifications, from 9 sections per group per stain as indicated in micrographs and exported to JPEG image format.

Image analysis

The images were analyzed using image J software. Manual cell counting and staining intensity were done using this software.

Cell counting

Using image J, the images were opened and the grid size (30000–50000 pixel^2) was chosen for comfortable counting of the 165 × 400 magnified images. The multi-point tool in the tool bar is selected. Counting was done manually by identifying and clicking on the specific cell types to count. The total number of cells count from each image was exported to excel for further analysis.

Statistical analysis

All quantitative data were analyzed using the GraphPad Prism® software (Version 8.4.2). Using 2-way ANOVA and subjected to Tukey's multiple comparisons test, with significance set at $p < 0.05$*. The outcomes were presented in scattered plots and bar charts with error bars to show the mean and standard deviation respectively.

Results

Differential sex-specific and dose-associated inflammatory effects following λ-cyhalothrin exposures

Quantitative analysis of the level of interleukin 1β (IL-1β) in the brain revealed a significant high IL-1β levels in the male rats that received a low dose (2 mg/kg) (p value = 0.0281), but not at high dose (4 mg/kg) (p value = 0.5642) of LCT when compared with the control (Fig. 1A). However, in female rats, low and high dose of LCT did not result in statistically significant change in the level of IL-1β (Fig. 1A).

On the other hand, exposures to LCT caused a sex- (p = 0.0223) and dose- (p = 0.0164) specific significant differences in the TNF-α levels, as revealed by the 2way ANOVA test (Fig. 1B). The differences manifested as a marked dose-dependent decrease in the female rats at low LCT (p value = 0.0261) and at high LCT (p value < 0.0001) when compared to the control (Fig. 1B). This data revealed a sex- and dose-dependent effects on inflammatory responses after exposure to LCT.

Distribution of Iba1+ microglia in hippocampal sub-regions following λ-cyhalothrin exposures

Next, we investigate the distribution of microglia in the hippocampal sub-regions (Cornu Ammonis (CA) 1 and 3) by immunostaining the microglia/macrophage-specific calcium-binding protein, Iba1, following exposure to low and high doses of LCT (Fig. 2). In the CA1, exposure to LCT did not significantly change the distribution of microglia in both sexes (low dose—p value = 0.8649, high dose—p value = 0.2103) when compared to the control (Fig. 2A and C). In the CA3 region, there is a dose-dependent significant increase in the number of microglia in the male rats but not in female (Fig. 2B and D) when compared with the control. This increase in the distribution of microglia is significantly higher in the male rats. The higher immunoreactivity in Iba1+ cells may indicate higher neuroinflammation in the hippocampal CA3 of male rats exposed to LCT.

λ-cyhalothrin exposure on the distributions of GFAP immunoreactive astrocytes in the hippocampus

Immunohistochemistry staining for glial fibrillary acidic protein (GFAP), a major protein constituent of astrocyte intermediate filaments and widely used marker of astrocytes, revealed a decrease in the number of astrocytes in the CA1 and CA3 areas of the hippocampus following exposure to LCT in both sexes compared to the control (Fig. 3). In the CA1, a significantly dose-dependent decrease in the number of astrocytes was observed in male rats exposed to low and high LCT (Fig. 3A and C). While in the females, there is no significant change in the low LCT (p > 0.9999), however, the high LCT resulted in a marked decrease in the number of astrocytes. (Fig. 3A and C).

Consistently, At the CA3, exposure to LCT led to a dose- and sex-dependent decrease in the distribution of the astrocytes (Fig. 3B and D). In male rats, a significant dose-dependent effect was observed when compared to the control while there was no difference in female rats at low and high LCT (Fig. 3D).

Parvalbumin expressed GABAergic interneurons in the hippocampus of λ-cyhalothrin exposed rats

Necrotic-like pathological features like reduced or shrink cell body, dendritic or cytoplasmic processes loss and relatively small size PV positive GABAergic interneurons were observed in the hippocampal sub-regions of

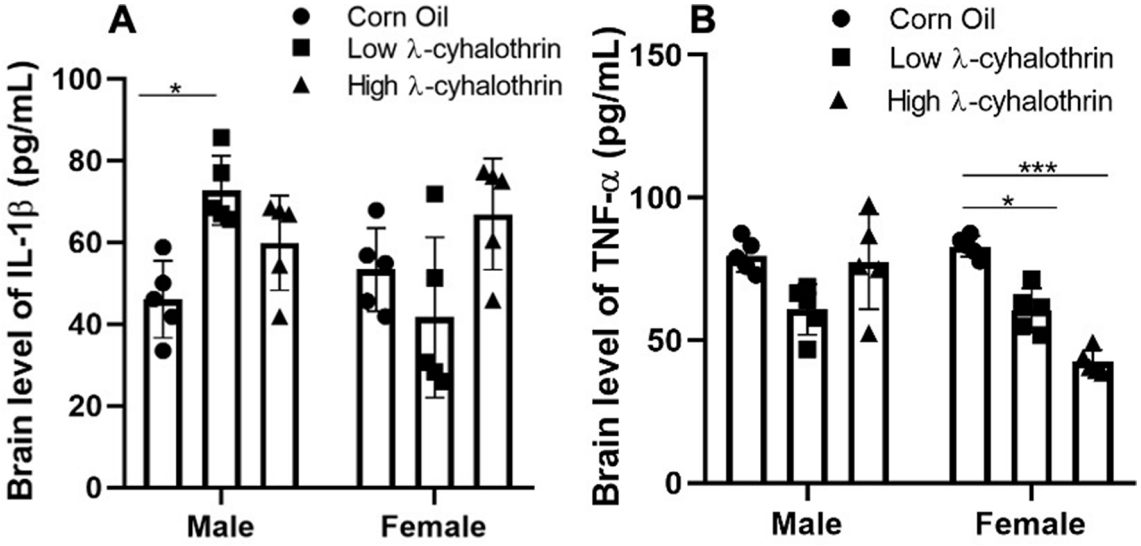

Fig. 1 Level of inflammatory biomarkers, IL-1β (**A**) and TNF-α (**B**) in Male and Female Wistar rats exposed to corn oil (control), low dose (2 mg/kg) and high dose (4 mg/kg) of λ-cyhalothrin respectively. Asterisks (*, ***) indicates significant (P < 0.05) higher than control. Bars are mean ± SD

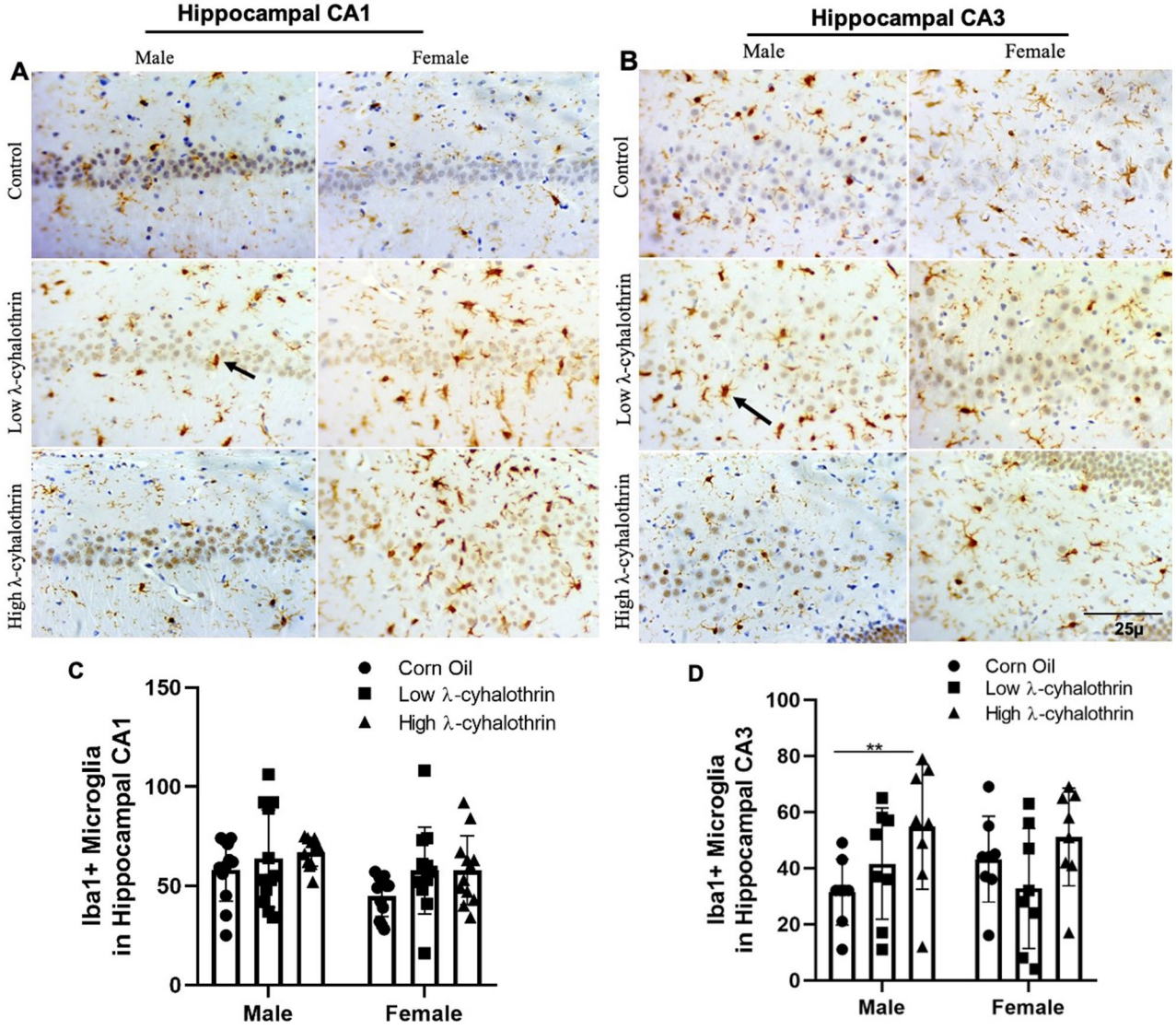

Fig. 2 Representative photomicrographs of Iba1 immuno-reactivity in the hippocampal CA1 (**A**) and CA3 (**B**), and the estimation of Iba1+ microglia in the hippocampal CA1 (**C**) and CA3 (**D**) of Male and Female Wistar rats exposed to corn oil (control), low dose (2 mg/kg) and high dose (4 mg/kg) of λ-cyhalothrin respectively (**=$p < 0.005$). Goat polyclonal Iba-1 (Abcam, USA, ab5076) at 1:250; X400, 25 μm

rats exposed to LCT (Fig. 4). These appear to be dose-dependent, as the above features are more frequently seen in the 4 mg/kg LCT exposed rats' hippocampus when compared with the lower dose and the control (Fig. 4). Although there is no distinction in sex specifically, the PV positive interneurons in the hippocampus of the female rats appeared to be most affected. The cell count (Fig. 4A) shows that there is no change in the number of parvalbumin positive interneurons the CA1 (Fig. 3C) and CA3 (Fig. 3D) of the male rats compared to the male control group. In the female rats, low LCT significantly decreased parvalbumin positive interneurons in the CA1 (Fig. 3C). Additionally, exposure to low and high LCT resulted in a marked decrease in the CA3 parvalbumin positive interneurons in female rats (Fig. 3D). Collectively, these findings indicate that exposure to LCT led to a decrease in the number of parvalbumin-positive interneurons in the hippocampal CA3 of female rats, which could consequently result in the alteration of the excitation/inhibition balance and hyperexcitability.

Discussion

λ-cyhalothrin could disrupt the nervous system functions, chemistry and morphology due to its lipophilic property and ability to cross the BBB. Insecticides including λ-cyhalothrin are known to induce their neurotoxicity by interfering with the chemical transmission of neurotransmitter. Thus, this research work studied GABAergic interneurons together with the inflammatory responses of the astrocytes and microglia involved in

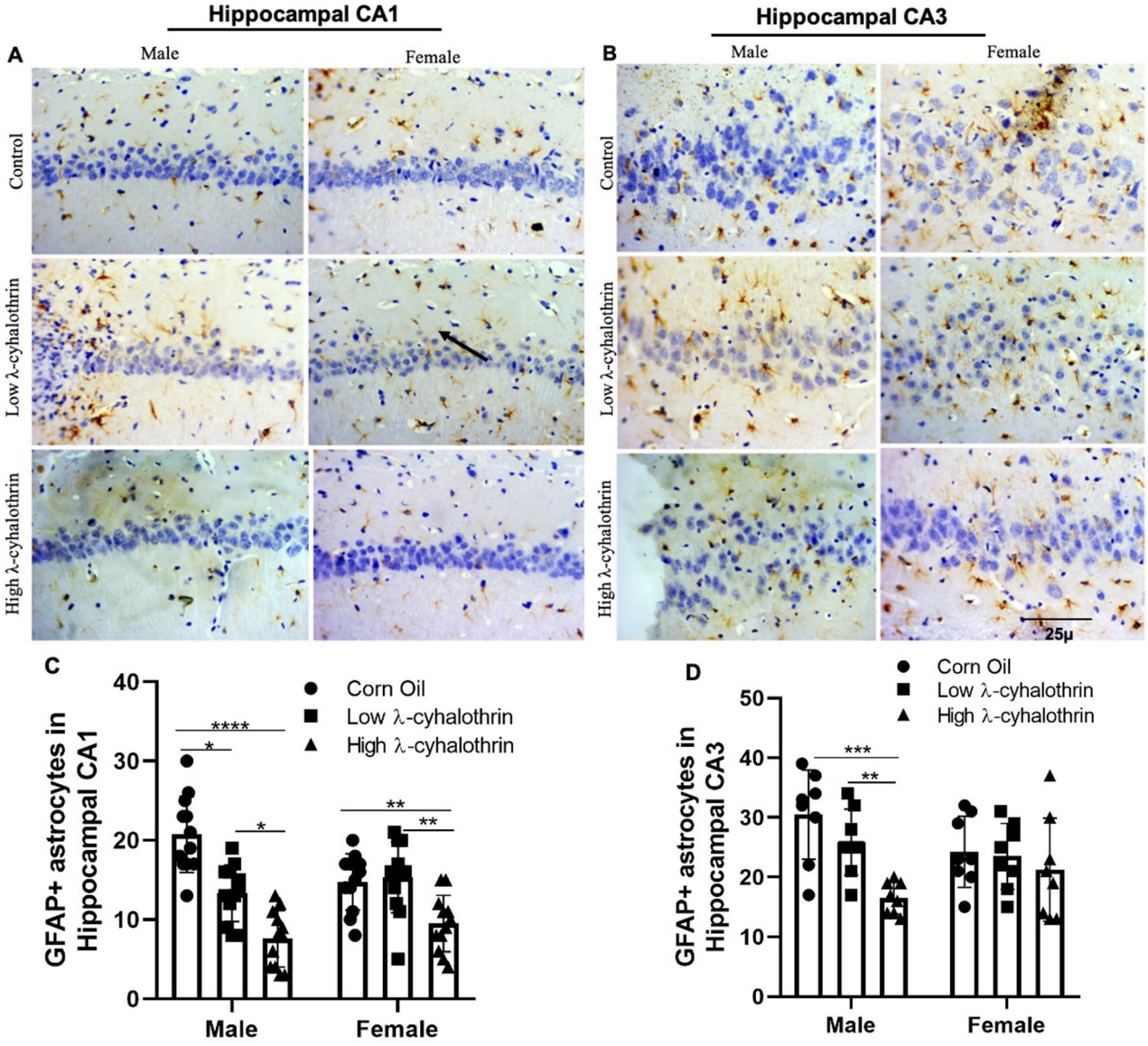

Fig. 3 Representative photomicrographs of GFAP immuno-reactivity in the hippocampal CA1 (**A**) and CA3 (**B**), and the estimation of GFAP + astrocytes in the hippocampal CA1 (**C**) and CA3 (**D**) of Male and Female Wistar rats exposed to corn oil (control), low dose (2 mg/kg) and high dose (4 mg/kg) of λ-cyhalothrin respectively (*, **, ***=$p < 0.005$). Mouse monoclonal GFAP-HRP conjugated (Santa Cruz, USA, 2E1: sc-33673) at 1:150; X400, 25 μm

maintaining homeostatic balances in the neurochemistry of the brain and physiological states.

Microglia is the resident macrophages in the brain, and they play a key role in preserving the normal function of the brain by constantly surveying the brain parenchyma to maintain homeostasis [25]. In response to exogenous insults, injury or stress, microglia secrete cytokines and other proteins for cell repair and regeneration [25]. These responses can be protective in form of M1 or M2 type microglia releases. In M1 form, microglia produce pro-inflammatory cytokines and proteins, which include TNF-α and IL-1β, and produces various neuroprotective chemicals like insulin-like growth factor 1 (IGF1) and brain derived neurotrophic factor (BDNF) in its M2 form [26]. Unregulated microglia activation most time leads to the production of free radicals, proinflammatory cytokines, and chemokines.

This study investigated the levels of two activated M1 microglia associated neuroinflammatory markers, TNF-α and IL-1β. Exposures to LCT led to a general increase in the levels of both TNF-α and IL-1β in the brains of all the exposed rats when compared to the unexposed control. This corroborates the findings in the study by Gomez-Gimenez [27], Gargouri [11] and their colleagues. Sex-specifically, the male brain markedly responded to the LCT insult by releasing more IL-1β when subjected to a comparative context with the females, while the females responded by dose dependent reduction in

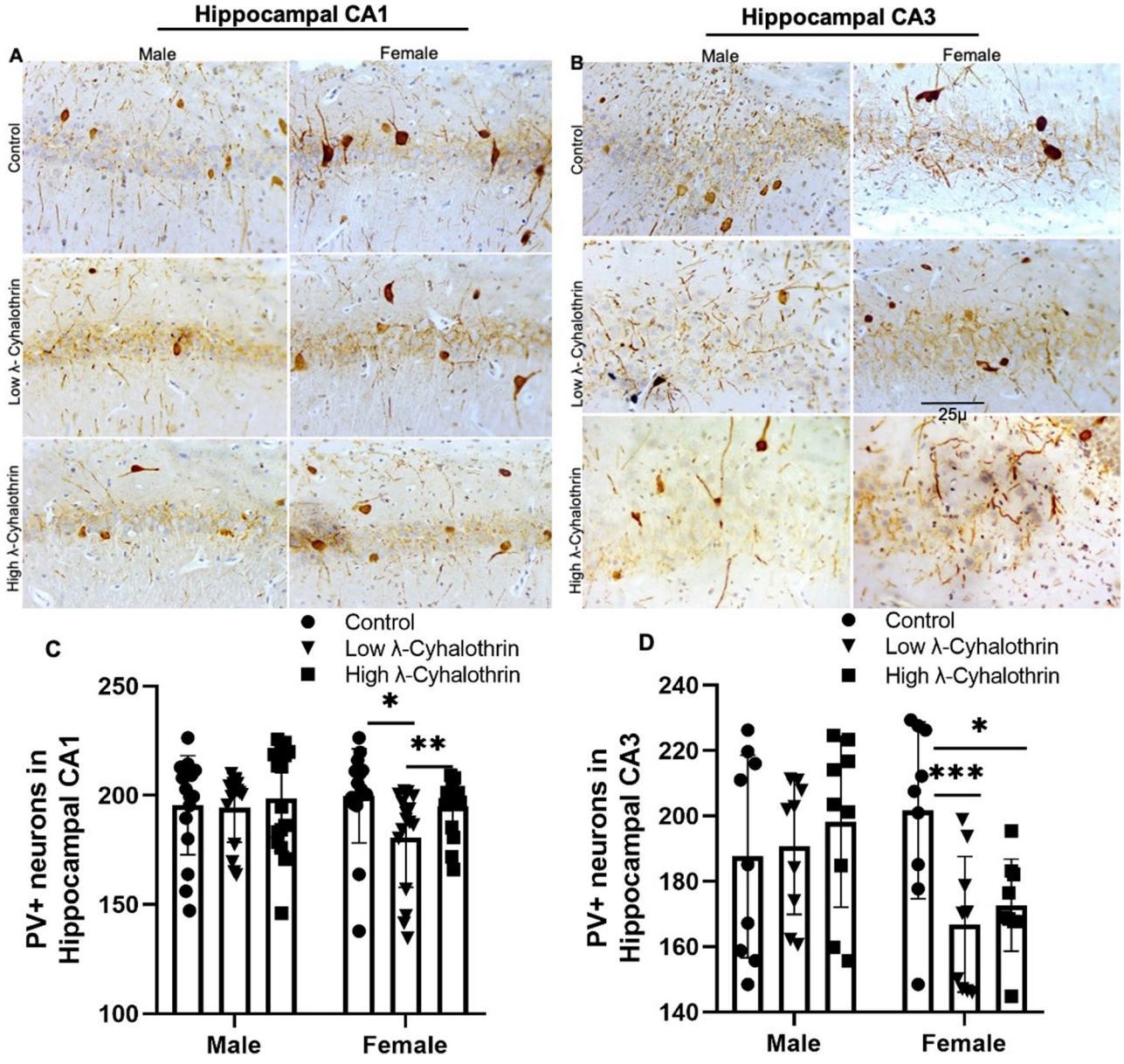

Fig. 4 Representative photomicrographs of PV immuno-reactivity in the hippocampal CA1 (**A**) and CA3 (**B**), and the estimation of PV + neurons in the hippocampal CA1 (**C**) and CA3 (**D**) of Male and Female Wistar rats exposed to corn oil (control), low dose (2 mg/kg) and high dose (4 mg/kg) of λ-cyhalothrin respectively (*, **, ***=$p < 0.005$). Rabbit polyclonal PV antibody (Novus Biologicals, USA, NB120-11427) at 1:1000; X400, 25 μm

TNF-α production. Although there is a relative pattern of induced production of IL-1β in both sexes, it is still unclear what contributed to the differential sex specificity to promote more release of IL-1β in the male, but a neuroprotective reduction of TNF-α in the female. These findings pose λ-cyhalothrin as a strong neurotoxic agent which may be implicated for various cognitive disorders where there are reported impaired hippocampal neuroplasticity [28].

As earlier mentioned, that the number of inflammatory cytokines and chemokines release correspond with the extent of microglia and or astrocyte activations. During neuroinflammation, microglia undergo phenotypic changes into active phenotypes from resting states to phagocytic phenotypic states, so as to enhance the clearing and phagocytosis of pathogenic cells and tissues [25]. Iba-1, a microglia-specific calcium-binding protein, was used to test for microglia-specific in this present study.

Iba-1 is a cross-linking protein that is specifically expressed in microglia and is upregulated whenever there is activation of the microglia. In this study, there was an increased distribution of Iba-1 immunoreactive microglia, in a comparably manner to other pesticides that are known to increase Iba-1 immunoreactivities, with an

example in BV-2 cell incubation in chlorpyrifos [29]. This microglia activation result in the release of large number of inflammatory mediators to induce an inflammatory response [29]. This response is alluded to by the response shown by IL-1β and TNF-α. Increased density of Iba-1 immunoreactive microglia was observed at all the hippocampal subfield. Iba-1 immunoreactivity was also observed to be greater in the hippocampus of the male LCT group, compared to that of the female group. This might be strengthened by the findings of Torres Rajan and his colleague who reported greater microglia proliferation in male exposed rats compared to the females [30].

Another frequently implicated pathological signs of neurotoxicity are reactive astrocyte or astrogliosis [29]. Proinflammatory markers released by the activated microglia trigger astrocytes leading to their activation [25], and this activation is characterized by the increased distribution of glial fibrillary acidic protein (GFAP) immunoreactive astrocytes. In this study, LCT induced neuroinflammation and caused increased distribution of microglia in the hippocampus of the exposed rats, which may indicate microglia activation in LCT neurotoxicity. GFAP immunoreactivities was not observed to be affected in both CA1 and CA3 subregions, suggesting that the induced inflammation may be independent of astrocytic activities. This is in contrary with what was previously reported following exposure to a type II pyrethroid deltamethrin, where increased GFAP intensity was noticed in the astrocytes [31]. Several studies have also shown that astrocytes activation alter the homeostatic functions of astrocytes such as potassium ion uptake, ion buffering, calcium ion signalling, and excitatory neurotransmitter uptake, which may in turn lead to apoptosis and neurodegeneration [32].

GABAergic interneurons are inhibitory neurons that release gamma-aminobutyric acid (GABA) neurotransmitter in order to regulate the firing rate of target neurons, thereby playing a vital role in neural circuitry and activity. Studies have shown a positive correlation between glia activation and GABAergic interneuron disruption [33, 34]. Calcium-binding proteins such as parvalbumin (PV), are used as markers for GABAergic neurons activity. In this study, λ-cyhalothrin caused marked reduction of PV immunoreactive inhibitory GABAergic interneurons in the hippocampus of the exposed animals, in a relative pattern to the observed activated microglia and astrogliosis in the same animals. The result showed reductions in the number of PV-expressing neurons in the hippocampal fields, especially CA3 subfield in the two exposed dosages of LCT, especially in the female rats, compared to PV-expression in the unexposed control. This confirms the inhibitory toxic effect of pyrethroids on GABAergic neurons [35]. There is also a greater reduction in PV-expressing interneurons in the hippocampus of the males compared to that of females, corroborating the male specific impairment in GABAergic receptor signalling previously reported [30]. These decrease in parvalbumin positive cells in males suggest a potential reduction of GABAergic interneuron function, which could lead to an imbalance in neural activity resulting to deficits in working memory and executive function, and is strongly associated with abnormalities in the hippocampus-related networks and neurological disorder related to hippocampal degeneration [36–38].

Conclusion

This research has shown that in both male and female alike, lambda cyhalothrin poses neuroinflammatory and activation of microglia. However, there are some differences in the effect exerted on each sex, although the differences in the effect on each sex may be related to difference in the number of glial cells in different regions or hormonal factors in male and female. In addition, the extent of the effects shown upon exposure to Lambda cyhalothrin differ in each hippocampal region, with the hippocampal CA1 appearing to be more vulnerable.

Abbreviations

LCT	λ-cyhalothrin
IL-1β	Interleukin 1 beta
TNF-α	Tumor necrotic factor alpha
Iba1	Ionized calcium binding adaptor molecule 1
GFAP	Glial fibrillary acidic protein
PV	Parvalbumin
GABA	Gamma-aminobutyric acid
BBB	Blood brain barrier
VGSC	Voltage gated sodium channels
GAD-67	Glutamate decarboxylase 67
NPY	Neuropeptide Y
SS	Somatostatin
UERC	University of Ilorin ethical review committee
IACUC	Institutional Animal Care and Use Committee
ELISA	Enzyme-linked immunosorbent assay
HRP	Horseradish peroxidase
DAB	3, 3 -diaminobenzidine
CA1	Cornu Ammonis 1
CA3	Cornu Ammonis 3
IGF1	Insulin-like growth factor 1
BDNF	Brain derived neurotrophic factor

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Author contributions

I.A., AM.I., and A.M.S.: Conceptualisations and design of the study, definition of intellectual content, experimental studies, literature search, collection of data, analysis and interpretation of data, manuscript preparation, editing and submission of manuscript. M.B., O.C., A.M.G. L.A., A.T.O., A.G.A., W.A.I., A.A.A., and O.M.J.: Experimental studies, literature search, collection of data and analysis, analysis and interpretation of data, manuscript editing and review and final approval of the version to be published.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
This research was approved by the University of Ilorin ethical review committee (UERC) (UIL/UERC/11/46KA072), following the recommendation of the College of Health Sciences ethical review committee, in compliance with the Institutional Animal Care and Use Committee (IACUC).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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