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Toxic Effects of Deltamethrin Doses on Antioxidative Defence Mechanism and Acetylcholinesterase Activity in Rat brain

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ABSTRACT
Aim: The present work was designed to study the dose dependent neurotoxic effect of Deltamethrin in Wistar rats. Deltamethrin is a type II pyrethroid insecticide. It is recommended for indoor spraying due to its high efficacy against a large variety of insects, low mammalian toxicity and easy biodegradability. There are recent reports of Deltamethrin induced system toxicity in laboratory animals. Materials and Methods: Different doses (2, or 3 or 6 mg/kg corresponding to 1/30th or 1/20th or 1/10th of LD_{50}) of Deltamethrin were administered to Wistar rats orally by gavaging for 28 days. Results: Deltamethrin caused a significant increase in lipid peroxidation (LPO), decrease in glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), glutathione S transferase (GST), glutathione reductase (GR), glutathione peroxidase (GPx) and acetylecholinesterase (AchE) in brain of rat. Histopathological studies showed neuronal degeneration, vacuolization and degenerated glial cells. Conclusion:The alteration in these parameters may be due to oxidative stress induced by Deltamethrin. Decrease in brain acetylecholinesterase (AchE) activity may be due to direct binding of Deltamethrin to AchE. The results indicated that the neurotoxic effect of Deltamethrin in male Wistar rats was dose dependent.

Keywords: Deltamethrin; brain; oxidative stress; acetylecholinesterase .

INTRODUCTION

Synthetic pyrethroides are widely used household insecticides, having high insecticidal activity against a variety of insects and low mammals toxicity. Increasing use of pyrethroid insecticides in agricultural and public health programmes has enhanced the chances of human exposure. [1-3]Deltamethrin is a type-II synthetic pyrethroid. It is helpful in eliminating and preventing a wide variety of household pests especially spiders, fleas, ticks, carpenter ants, bees, cockroaches and bedbugs. Deltamethrin produces a complex poisoning syndrome, and acts on a wider range of tissues in insects. Although considered non toxic to mammals, recent studies have shown adverse effect of Deltamethrin on nervous, [4] hepatic & renal [5] and male reproductive system [6] in laboratory animals. The reports of neurotoxicity of Deltamethrin in rodent models are a major concern. Deltamethrin has been reported to possess high affinity for the central nervous system (CNS) and neuronal sodium channels were found to be the primary targets in both insects and mammals.[7-9] Deltamethrin exerts its neurotoxic effects by modifying sodium channel kinetics leading to altered synaptic transmission and neuroexcitation.[10,11] Studies have reported persistent changes in learning,[12]motor behaviour,[13] muscarinic acetylcholine receptor binding [14,15] and blood–brain barrier permeability [16,17] in rats and mice following prenatal exposure to Deltamethrin and other pyrethroids. Prenatal exposure to different doses (0.25, or 0.5 or 1.0 mg/kg corresponding to 1/320th or 1/160th or 1/80th of LD50) of Deltamethrin to the pregnant Wistar rats from gestation day 5 to 21 were found to produce a dose dependent increase in the activity of cytochrome P450 (CYP) dependent 7-ethoxyresorufin-O-deethylase (EROD), 7-pentoxyresorufin-O-dealkylase (PROD) and N-nitrosodimethylamine demethylase (NDMA-d) in brain and liver of offspring postnatally at 3 weeks. The data suggests that low dose prenatal exposure to Deltamethrin has the potential to produce long lasting effects on the expression of xenobiotic metabolizing cytochrome P450s in brain and liver of the offspring [18]. The effects of prenatal exposure of rat pups to 0.08 mg/kg Deltamethrin (DTM) on physical, reflex and behavioral developmental parameters, on forced swimming and open-field behaviors, and on striatal monoamine levels at 60 days of age were observed by Lazarini *et al*. [19] Asari *et al.* [20] studied the effect of early neonatal exposure to low doses 1mg/kg of Deltamethrin on the histogenesis of the cerebellar cortex.

The present study was planned to investigate the toxic effects of Deltamethrin doses on antioxidative defence mechanism and acetylcholinesterase activity in rat brain.

Materials and Methods:

Animals

Male Wistar rats, weighing about 150-200 gm, were used in the experiments. Animals were obtained from Central Drug Research Institute (CSIR), Lucknow, India and were kept for acclimatization in the animal house at ambient temperature of $25^0C\pm 2^0C$ and 45-55% relative humidity, with 12h each of dark and light cycles. Animals were fed pellet diet and water *ad-libitum*. All the experiments were carried out in compliance with the guide for the care and use of laboratory animals. The experimental protocols approved by Institutional Animal Ethical Committee (IAEC) vide reference number BU/Pharma/IAEC/11/042.

Chemicals

Technical grade (99%) pure Deltamethrin was gifted by Gharda Chemicals Lt. Mumbai, India. All other chemicals used in this study were of high purity.

Treatment Schedule

Male Wistar rats (24) were divided into 4 groups of six rats eAchE. Deltamethrin was dissolved in DMSO (0.5ml) and administered daily orally by gavaging in Wistar rats as described below:

G-A. Control Normal diet and water *ad libitum* for 28days

G-B. Exposure I Deltamethrin 1/30 of LD_{50} (2mg/kgbw) for 28 days

G-C. Exposure II Deltamethrin 1/20 of LD_{50} (3mg/kgbw) for 28 days

G-D. Exposure III Deltamethrin 1/10 of LD_{50} (6mg/kg bw) for 28 days

At the end of the experiment, rats were sacrificed. Whole brain was removed and weighted. Part of brain was used for estimation of lipid peroxidation, enzymatic, non enzymatic antioxidants and acetylcholinestrase activity.

Biochemical Estimations

Preparation of Homogenate

Brain was homogenized with 10 % (w/v) homogenizing buffer (0.1 M phosphate buffers, pH 7.4+150mM Kcl). Part of the homogenate was used for LPO and GSH estimations. The remaining homogenate was centrifuged at 9000 rpm for 20 min. to get supernatant (S) fraction. The supernatant (S) obtained was used for SOD, CAT, GPx, GR, GST and protein estimations.

Lipid Peroxidation (LPO)

LPO was estimated as described by Okhawa et al. [21]. 1ml homogenate was incubated at 37^0 c for 10 min.1 ml of 10% (w/v) chilled trichloroacetic acid (TCA) was added to it and centrifuged at 2500 rpm for 15 min at room temperature. 1 ml of 0.67% Thiobarbituric acid (TBA) was added to 1 ml of supernatant and kept in boiling water bath for 10-15 min. The tubes were cooled under tap water, followed by addition of 1ml of distilled water. Absorbance was recorded at 530 nm and the results were expressed as n moles MDA/hr/g tissue.

Reduced Glutathione (GSH)

Reduced glutathione was estimated by the method described by Ellman [22]. 1 ml of 10% crude homogenate was mixed with 1 ml of 5% TCA (w/v), the mixture was allowed to stand for 30 min. and centrifuged at 2500 rpm for 15 min. 0.5 ml of supernatant was taken and 2.5 ml of 5'5 '-dithionitrobenzoic acid (DTNB) was added, mixed thoroughly and absorbance was recorded at 412 nm. The results were expressed as µmoles/g tissue.

Superoxide Dismutase (SOD)

SOD was estimated by the method described by Kakkar et al. [23]. 650 µl of sodium pyrophosphate buffer, 50 µl Phenazine Methasulphate (PMS), 150 µl of Nitroblue tetrazolium chloride (NBT) and 100 µl NADPH were added to 50 µl of 'S'. The mixture vortexed thoroughly, incubated for 90 sec and 500µl glacial acetic acid was added to stop the reaction. 2.0 ml of n-butanol was added to the mixture, vortexed thoroughly and kept at room temperature for 10 minutes. Absorbance was measured at 560 nm and the results were expressed as µmoles /min/mg protein.

Catalase (CAT)

Catalase was estimated by the method of Sinha et al. [24] 1ml of phosphate buffer and 0.4 ml water was added to 0.1 ml of 'S'. Reaction was started by adding 0.5 ml H_2O_2 and mixture was incubated at 37^0C for 1 min. Reaction was stopped by adding 2ml of dichromate : acetic acid reagent (1:3) and kept at boiling water bath for 15 min. The mixture was cooled and absorbance was read at 570 nm. Catalase activity was calculated in terms of µmoles/min/mg protein.

Glutathione Peroxidase (GPx)

GPx was estimated by the method of Rotruck et al. [25]. 0.4 ml Tris HCl buffer, 0.2 ml GSH, 0.1 ml water, 0.2 ml H_2O_2 and were added to 0.1ml 'S'. The mixture was incubated at 37ºC for 15 min and 0.5 ml TCA (10%) was added. The mixture was centrifuged at 2000 rpm for 15 minutes, 0.5 ml of supernatant was taken and 2 ml di-sodium hydrogen phosphate buffer and 0.5 ml Ellman's Reagent were added. Absorbance was read at 420 nm. The results were expressed as nmoles/min/mg protein.

Glutathione Reductase (GR)

Glutathione reductase was estimated by the method described by Carlberg and Mannervik [26]. 2.5ml of buffer (pH 6.6), 0.2ml NADPH and 0.2ml Glutathione disulfide GSSG and 0.1 ml supernatant (S) were mixed and allowed to stand for 30 seconds. Absorbance was recorded at 340 nm for 3 minutes at 30 seconds intervals. GR was calculated in terms of n mol/min/mg protein.

Glutathione-S-Transferase (GST)

GST was estimated as per method of Habig et al. [27]. The reaction mixture consisting of 1.425 ml phosphate buffer (0.1 M, pH6.5) 1.475 ml GSH (1.0 mM), 20µl 1-chloro-2,4-Dinitrobenzene (CDNB,1mM) and 60 µl water were added to 20µl of 'S' to give 3.0 ml of reaction mixture. Absorbance was recorded at 340nm

and the GST activity was calculated as µmoles CDNB conjugate formed /min/mg protein using molar extinction coefficient of $9.6x10^3M^{-1}$ cm^{-1}.

Total Protein (TP)

Protein was estimated by the method of Lowry et al [28]. Distilled water (0.49 ml) was added to 0.01 ml of S fraction of brain in a test tube containing 2.5 ml of alkaline solution Incubated for 10 min at room temperature. After 10 min incubation, 250 µl of folin reagent (FCR) was added, and again incubated for 30 min. at room temperature. After incubation absorbance was read at 600nm.

Acetylcholinestrase (AchE) Activity

Acetylcholinesterase assay was estimated by Ellman et al [29]. Brain was weighed and homogenized into 0.1M phosphate buffer (pH 8.0). 0.4 ml aliquot of the homogenate was added to a cuvette containing 2.6ml phosphate buffer (0.1M, pH 8.0) and 100µl of DTNB. The contents of the cuvette were mixed thoroughly by bubbling air and absorbance was measured at 412nm. When absorbance reaches AchE a stable value, it was recorded as basal reading. 20µl of substrate i.e. acetylthiocholine was added and change in absorbance was recorded for a period of 10 min at 2 minutes interval. Change in the absorbance/minute was determined. The results were expressed as nmole/min/gm tissue.

Histological Studies

Brain of eAchE rat was removed and quickly fixed in Bouin's fluid for at least 24 h. Fixed materials were embedded in paraffin wax, sectioned at 5 micrometres and stained with Mayer's haematoxylin and eosin (HE) for histological examination.

Statistical Analysis

Results were expressed as Mean ± SEM. Data was subjected to one way analysis of variance (ANOVA). The treatment groups were compared with control group using Dunnett's test. All the statistics were carried out in GraphPad InStat Software Inc., v. 3.06, San Digeo, USA.

Results:

Brain Weight

Deltamethrin caused a non-significant (P>0.05) decrease in brain weight in group B (0.841), group C (1.383) and group D (2.164%) as compared to group A (Figure 1).

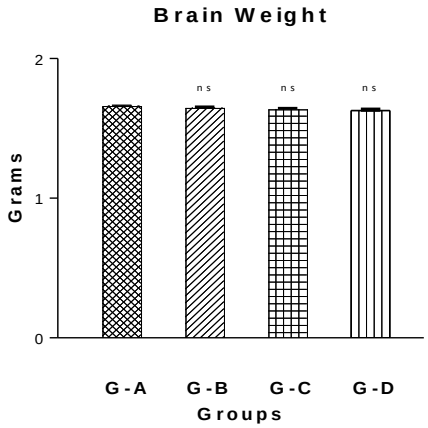

Figure 1: Dose dependent effect of Deltamethrin on brain weight of Wistar rats. The values represents as Mean ± SEM for 6 rats each. ns =P>0.05 as compared with control value. G-A,Control; G-B, Exposure I; G-C, Exposure II; G-D, Exposure III.

Lipid peroxidation, Non- enzymatic and Enzymatic antioxidants

Lipid peroxidation level increased significantly (P<0.01) in group B (35.83%), group C (121.28%) and group D (183.52%) as compared to group A. GSH level showed a significant (P<0.01) decrease in group D (53.04%), and group C (25.28%). On the other hand, a significant (P<0.05) decrease in GSH level was observed in group B (19.41%). In brain, a significant (P<0.01) decrease in SOD and CAT activity in group B (11.93, 8.19%), C (20.23, 12.58%) and group D (36.52%, 36.49%) were observed respectively when compared with group A. Group B showed a significant (P<0.05) decrease in GPx (27.96 %), GR (95.37 %) and GST (45.45%) activity as compared to group A. GPx, GR and GST activity decreased significantly (P<0.01) in group C (21.22, 20.95, 22.25%) and group D (13.17, 8.77 and 12.46 %) respectively. Total Protein levels in brain were non significantly (P>0.05) increased in group B (1.75 %) and group C (6.57%) however a significant (P<0.01) increase was observed in group D (14.035 %) as compared to group A (Table 1).

Parameter	G-A	G-B	G- C	G-D
LPO (nmoles MDA/hr/gm tissue	1.560±0.016	2.119±0.007**	3.452±0.014**	4.424±0.010**
GSH (µmole/gm tissue)	0.443±0.028	0.357±0.026*	0.331±0.023**	0.208±0.013**
SOD (nmole/min/mg protein)	64.321±0.010	56.643±0.018**	51.303±0.062**	40.825±0.036**
CAT (µmole/min/mg protein)	66.812±0.007	61.335±0.016**	58.402±0.019**	42.428±0.017**
GPx (nmole/min/mg protein)	0.683±0.016	0.593±0.020*	0.538±0.021**	0.492±0.024**
GR (nmole/min/mg protein)	1.470±0.039	1.341±0.012*	1.162±0.032**	0.068±0.009**
GST (nmole/min/mg protein)	2.462±0.049	2.155±0.088*	1.914±0.032**	1.343±0.012**
Total Protein (mg/ml)	0.228±0.004	0.232±0.005ns	0.243±0.004ns	0.255±0.005**

Table 1: Dose dependent effect of Deltamethrin on lipid peroxidation, non- enzymatic and enzymatic antioxidants in brain of Wistar rats. The values represents as Mean ± SEM for 6 rats each. **=P<0.01, * = P<0.05, ns=P>0.05 as compared with control value. G-A,Control; G-B, Exposure I; G-C, Exposure II; G-D, Exposure III.

Acetylecholinesterase activity

The present study showed that Deltamethrin administered to the Wistar rats resulted in a significant decrease in brain AchE activity in group C (P<0.01, 29.31%) and group D (P<0.001, 72.98%), whereas a non-significant (P>0.05) decrease was

observed in group B (10.91%) as compared to group A (Figure 2).

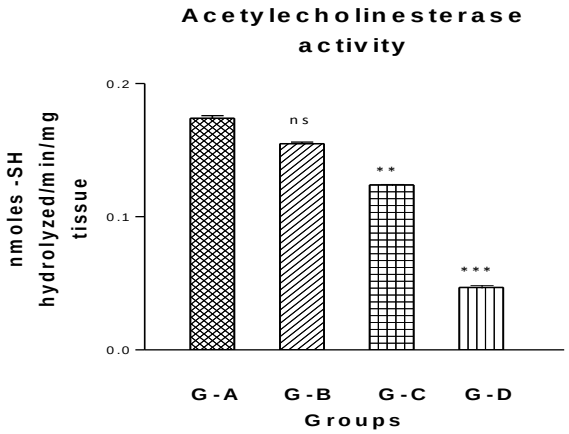

Figure 2: Dose dependent effect of Deltamethrin on acetylcholinestrase activity in the brain. The values represents as Mean ± SEM for 6 rats each. ***= P<0.001, **=P<0.01, ns=P>0.05 as compared with control value. G-A,Control; G-B, Exposure I; G-C, Exposure II; G-D, Exposure III.

Brain Histology

In G-B, dose of 2mg/kg produced mild neuronal degeneration and vacuolization in the cerebral hemisphere in rats on 28 days. Dose (3mg/kg) of Deltamethrin in G-C produced neuronal degeneration ,vacuolization and necrosis with degenerated glial cells. Higher dose (6mg/kg) of Deltamethrin in G-D produced total neuronal degeneration, more vacuolization and degenerated glial cells as compared to G-A (Figure 3).

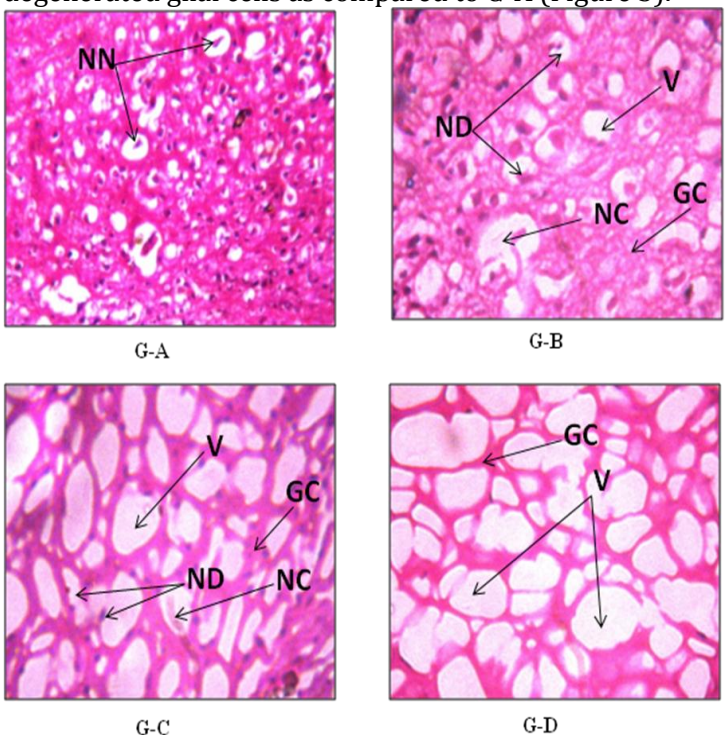

Figure 3: Dose dependent effect of Deltamethrin on histology of brain (cerebrum). NN=normal neurons; GC=glial cells; NC=necrosis; ND=neuronal degeneration; V=vacuole

Discussion:

The main mechanism of action of Deltamethrin involves the inhibition of acetylcholinestrase [30,31] resulting in a cholinergic syndrome [32].

Brain is highly susceptible to environmental changes and toxicants. It is more vulnerable to oxidative stress as compared to other organs of the body as it consumes high amount of oxygen, contains high amounts of PUFA and low levels of antioxidant enzymes [33]. There are reports that chromic exposure of DM may cause may cause neurotoxicity in human subjects. Owing to its lipophilic nature, Deltamethrin may have an easy as well as rapid access to brain. Accumulation of Deltamethrin in brain even in the very small doses can produce significant toxicological effects. The present study was carried out to assess dose dependant neurotoxic effect of DM in Wistar rats. Earlier reports of dose dependant exposure of DM to male rats increased Nrf2 protein in the nuclear fraction of cerebral cortex and cytoplasmic fraction of hippocampus tissue of brain. Increase in Nrf2 protein was dose dependant with 12.5mg/kgbw of DM exhibiting more increase as compared to 3.13 mg/kgbw [34]. Repeated dose toxicity of DM at 15mg/kgbw altered the biochemical parameters in liver of male Wistar rats. It decreased cytochrome P450 and other antioxidant molecules. The biochemical changes were correlated with histological changes [35].

In the present study brain weight decreased non-significantly due to administration of different doses of Deltamethrin. The marginal decrease in brain weight may be due to brain damage caused by accumulation of Deltamethrin [36, 37]. The LPO level in brain increased significantly. Deltamethrin exposure increases oxidant species resulting in irreversible oxidation reaction which lead to chemical modification of biological processes. The hydroxyl radical can initiate lipid per oxidation which is a free radical chain leading to loss of membrane structure and function [38, 39]. Increase in LPO and generation of ROS may reduce cell viability. Increase in lipid peroxidation in rat brain has been reported earlier on chlorpyrifos and Deltamethrin exposure [4]. Increase in LPO level has also been observed in liver, kidney and brain of rats exposed to cypermethrin by Sankar et al. [40].

Different doses of Deltamethrin decreased the GSH level in brain as compared to control. The decrease in GSH level may be due to the oxidative stress produced by Deltamethrin or due to inhibition of enzymes such as GR, GPx which leads to depletion of levels of GSH. Significant decrease in SOD activity was observed on DM exposure. The decrease in SOD activity may be due to imbalance between oxidants and antioxidants as delltamethrin exposure produces oxidative stress and increases the production of free radicals. These free radicals may be attacking the thiol group of cysteine residues and polysaturated fatty acids of biological membranes. The decreased level of SOD has been reported by Li et al. [41] in the nervous system of rats exposed to Deltamethrin and Olawale et al. [42] in the brain of rats fed with diet containing permethrin. Deltamethrin administration decreased the activity of CAT in rat brain, which may be due to increased hydrogen peroxides by Deltamethrin exposure. Yousef

et al. [43] reported the decreased CAT activity in rats exposed to Deltamethrin.

Different doses of Deltamethrin decreased the GPx activity in brain of rats. The decrease in GPx activity may be due to reduced activity of glutathione (over production of free radicals) which is used as substrate for GPx. Similar results were reported by Sun et al. [44]. in the rat brain exposed to Deltamethrin. Decrease in the GR and GST activity has been observed in this study. Decrease in GR activity have already been reported by Sharma and Singh [45] in the rat brain exposed to dichlorvos and lindane. The activity of GST in rat brain decreased due to different doses of Deltamethrin which might be due to oxidative stress produced by Deltamethrin which in turn alter the normal enzymatic function. These results were supported by Singh et al. [46] who reported decrease in the GST of brain due to beta-cyfluthrin administration. These results were also supported by the Johri et al. [18] in rat brain after Deltamethrin treatment.

Total protein levels in rat brain were decreased in Deltamethrin exposed groups. The decrease in the total protein may be due to depletion in the level of various antioxidant enzymes and decrease in cell viability. Decrease in total protein in brain has been reported earlier on administration of dieldrin and malathion [47].

Decrease in acetylcholinestrase activity was observed on Deltamethrin exposure. The inhibition of acetylcholinestrase by Deltamethrin may be related to the fact that pyrethroids potentially inhibit neurotransmitter metabolizing enzymes in the brain, which are essential for maintaining the balance of neurotransmitter like AchE in the brain; leads to decrease in the activity of AchE levels [48]. Decrease in acetylecholinesterase activity has been reported previously who on exposure to cyfluthrin [38], chlorpyrifos and Deltamethrin [4] and chlorpyrifos and cypermethrin [49].

Acetylcholinesterase is a serine protease that hydrolyzes the neuro-transmitter acetylcholine. AchE is found at mainly neuromuscular junctions and cholinergic brain synapses, where its activity serves to terminate synaptic transmission. The structural studies of AchE indicates the presence of different binding sites, one, a selective aromatic cation binding site; two, esteratic site and three, peripheral anionic substrate binding site. The AchE molecule interacts both with esteratic and anionic sites. The active site of AchE is mainly constructed by Phe (338), Try (86), Ser (203), Glu (327) and His (440) residues (Figure 4). Trp and Phe constitute the cationic where as Ser and His constitute the esteratic binding site of the enzyme. Neurotransmitter acetylcholine binds with both esteratic and anionic sites of AchEE. The presence of aromatic amino acids in the active site of the enzyme also creates a hydrophobic region. It is assumed that pyrethroids including Deltamethrin may interact with this hydrophobic region and cause inhibition in AchE activity.

Our observation reveals that repeated oral administration of different doses of Deltamethrin showed neuronal degeneration with vacoulization, degenerated glilial cells and necrosis. The observed sign showed that nature and intensity of toxic symptoms produced by Deltamethrin are dose and time dependent. Neuronal damage with glilial cells proliferation on repeated dose exposure of cypermethrin has been reported [37].

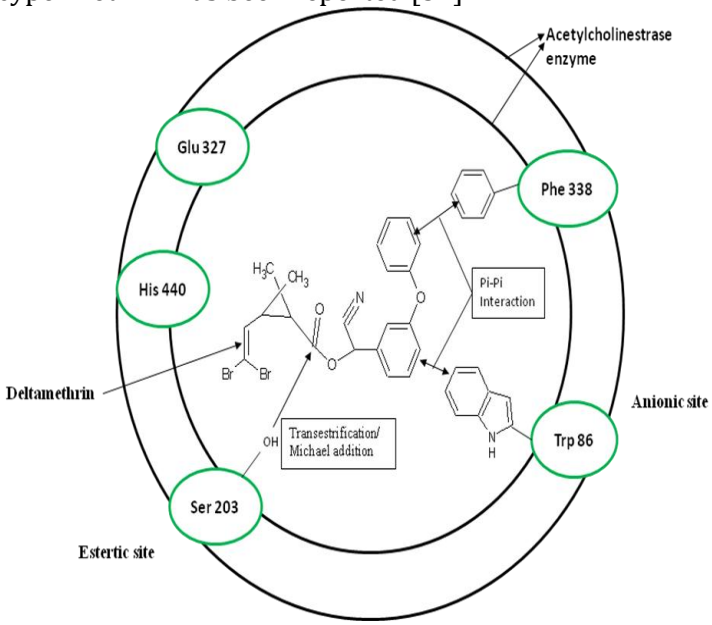

Figure 4. Possible binding sites of Deltamethrin with acetylecholinesterase

The present study showed that Deltamethrin caused considerable toxicity to Wistar rat brain. The toxicity was dose dependent and the high dose was more toxic as compared to low doses. Deltamenthirn induced neurotoxicity was mediated through free radical formation, reduced antioxidant defence mechanism and inhibition of acetylcholinestrase activity (AchE). The AchE inhibitory activity of Deltamethrin may be by interacting with the anionic binding site of the AchE enzyme.

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