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REGIONAL CATECHOLAMINE CONCENTRATIONS IN BRAIN AND SPINAL CORD OF MALE ALBINO RATS TREATED WITH THE SYNTHETIC PYRETHROID CYFLUTHRIN

By

Nawal A. Ahmed[1], Nagi A. Ibrahim[2*], Al-Ahmady S. Al-Zahaby[3] and Safaa A. Al-Zawahry[3]

1- Department of Biology, Faculty of Science, United Arab Emirates University, Al-Ain, U. A. E.

2- Biomedical Programme, Faculty of Science, Qatar University, Doha, Qatar.

3- Department of Zoology, Faculty of Science, Zagazig University, Zagazig, Egypt.

تركيز الكاتيكولامينات في الدماغ والحبل الشوكي لذكور الجرذان البيضاء المعالجة بالمبيد الحشري البيريثرويدي «سفلوثرين»

نوال عبد الحي أحمد و ناجي علي إبراهيم و الاحمدي شفيق الذهبي و صفاء أحمد الظواهري

تناول البحث دراسة تأثير الحقن المتكرر في التجويف البريتوني لذكور الجرذان البيضاء بالمبيد الحشري البيريثرويدي سفلوثرين على تركيزات الدوبامين والنورابينفرين والابينفرين في مناطق محددة من الدماغ والحبل الشوكي.

تم حقن الجرذان بثلاثة جرعات منفصلة من السلفوثرين تعادل ١ / ٤ ، ١ / ٨ ، ١ / ٥٠ الجرعة المميتة لنصف المجموعة، حيث تم الحقن بالجرعة الاولى يوم بعد يوم لمدة ١٨ يوم، أو يومياً بأي من الجرعتين الثانية والثالثة لمدة ١٨ يوم و٦ أسابيع على التوالي.

تم قياس تركيزات الدوبامين والنورابينفرين والابينفرين في أنسجة الفص الشمي، تحت سرير الدماغ (الهيبوثالامس)، المخيخ، النخاع المستطيل، والمنطقتين الصدرية والقطنية من الحبل الشوكي بعد ٣، ٦، ٩، ١٢، ١٥، ١٨ يوماً من المعالجة بأي من الجرعتين ١ / ٤ ، ١ / ٨ الجرعة المميتة لنصف المجموعة، وبعد ١، ٢، ٣، ٤، ٥، ٦ أسابيع من المعالجة بالجرعة ١ / ٥٠ الجرعة المميتة لنصف المجموعة.

أظهرت النتائج أن معالجة الجرذان بأي من الجرعات المستخدمة قد أحدث زيادة في تركيزات الدوبامين والنورابينفرين والابينفرين في جميع المناطق المدروسة من الدماغ والحبل الشوكي، حيث أعتمدت مستويات الزيادة على فترات المعالجة بالحقن وأيضاً على المنطقة المدروسة.

أقترحت الدراسة أن للسفلوثرين تأثيرات سامة على الجهاز العصبي المركزي في الثدييات، تتمثل في أحداث تغييرات في تركيز الكاتيوكولامينات في مناطق مختلفة من الدماغ والحبل الشوكي.

Key-words : Insecticides, Pyrethraids, Cyfluthrin, Catecholamines, Nervous System, Neurotoxicity.

ABSTRACT

The principal objective of this study was to determine the modifications induced by the synthetic pyrethroid insecticide cyfluthrin in the concentrations of dopamine (DA), norepinephrine (NE) and epinephrine(E) in selected brain and spinal cord regions of male albino rats. A group of 30 rats were injected intraperitoneally every other day with cyfluthrin at 1/4 LD50 dose level for 18 days. Other two groups (30 rats each) were daily given cyfluthrin intraperitoneally at the dose levels of 1/8 LD50 and 1/50 LD50 for 18 days and 6 weeks respectively. All treated animals developed a time and dose dependent toxicity symptoms and behavioural changes representing the typical CS syndromes produced by α- cyano pyrethroids . These involve skin paresthesia , body tremor , motor incoordination , choreoathetotic writhing and profuse salivation . Clonic and tonic seizures appeared at the terminal stages .

Concentrations of DA, NE and E were measured in the olfactory bulb, hypothalamus, cerebellum, medulla oblongata, thoracic and lumbar regions of the spinal cord homogenates of rats treated for 3, 6, 9, 12, 15 or 18 days every other day or daily with 1/4 or 1/8 LD50 dose levels respectively and of rats treated daily for 1, 2, 3, 4, 5 or 6 weeks with 1/50 LD50 dose level.

It was found that cyfluthrin at all dose levels used induced a general increase of DA, NE and E in all studied brain and spinal cord regions. The pattern of this increase was both time and regional dependent. These data suggest that cyfluthrin is a mammalian neurotoxic agent, and the severity of its toxic action is dependent on the treatment period as well as the affected region of the central nervous system.

* Person to whom Correspondance Should be Made.

INTRODUCTION

Pyrethroids are synthetic insecticides which worldwide increasingly replace organochlorine and organophosphate insecticides in fields like agriculture, hygienics, household, wear and building industry. Being lipophilic and strongly neurotoxic substances (Casida et al., 1983; Dorman and Beasley, 1991; Eriksson and Fredriksson 1991; Ahmed et al., 1995), a considerable health risk has been predicted in regard of their application.

In previous studies on the pyrethroid-induced mammalian toxicity, two distinct syndromes of their toxic action have been described in mice and rats. Type-I syndrome (T-syndrome) produced by pyrethroids lacking the α–cyano substituent and is characterized by restlessness, incoordination, prostration, elevated startle response, whole body tremor (Verschoyle and Aldridge, 1980; Dorman and Beasley, 1991). The Type II syndrome (CS-syndrom) is produced by pyrethoids containing the α–cyano substituent and elicits ataxia, intense hyperactivity, burrowing behavior, coarse tremors, clonic seizures, choreoathetosis and profuse salivation (Ray and Cremer, 1979; Brodie and Aldridge, 1982; Dorman and Beasley, 1991; Husain et. al., 1996).

It has been evidently noted that Type I syndrome originates in the brain and many have also peripheral component, whereas, Type II syndrome may act exclusively at a site located in the central nervous system (Casida et al., 1983).

In mammals, it has been extensively shown that the insecticide induced behavioral abnormalities exclusively correlated with alterations of brain concentration of certain neurotransmitters and their metabolites and the activity of their metabolizing enzymes. This correlation was observed in experimental animals exposed to different groups of insecticides including, organophosphates (Chanada and Pope, 1996; Santhoshkumar et al., 1996), organochlorines (Ho et al., 1981; Hong et al., 1984 ; Chen et al., 1985 ; Hudson et al., 1985; Sunol et al., 1988 a, b) , carbamates(Kobayashi et al., 1985) and pyrethroids (Nishimura et al., 1984; Husain et al., 1996).

Catecholamines usually imply dopamine (DA) and its metabolic products norepinephrine (NE) and epinephrine (E). The main sites of catecholamine production in mammals are chromaffin cells of the adrenal medulla, sympathetic neurones and localized collections of neurones within the brain (Chattoraj and Watts, 1987; Weinkove, 1988).

In the mammalian central nervous system, catecholamines represent a group of neurotransmitters that are involved in the control of a wide variety of body functions including, coordination and integration of fine body movement and balance, memory, emotion, hunger, thirst, temperature regulation, blood pressure maintenance, sleep, mood elevation and depression, reproduction and behavior (Whitley et al., 1994).

Data collected from previous neurochemical studies on the level of brain catecholamins in rats or mice treated with different membres of insecticides have been a quite contradictory. In animals treated with different organophosphorus insecticides, it has been shown that chlorfenvinphose, dichlorvos or fenitrothion induced a marked diminution of brain NE level (Brzezinski and Wysocka, 1980), whereas elevation of brain DA level was observed in rats treated with leptophos (Aldous et al., 1982), and a significant increase of brain DA, NE and E levels was recorded following the adminstration of nuvacron into mice (Gupta et al., 1984). Various organochlorine inseticides similarly showed non consistent effects, while chlordecon did not affect the whole brain level of DA in rats (Hong et al., 1984), it decreased the NE concentration in the rat hypothalamus (Chen et al., 1985). Adminstration of DDT to rats did not induce any change in brain NE level (Hong et al., 1985). Moreover, treatment of rats with lindane increased the DA level in mesencephalon (Sunol et al., 1988 a), but decreased the NE concentration in the partial cortex (Sunol et al., 1988 b). The carbamate furadan induced a significant increase in the level of DA, NE and E in mouse whole brain (Gupta et al., 1984). The pyrethroid fenvalerate induced a pronounced decrease of brain DA and NE levels in adult female rats (Husain et al., 1991), but increased markedly the brain DA level in neonatal rats (Malaviya et al., 1993).

Cyfluthrin is an-cyano synthetic pyrethroid sold under the trade marks Solfac, Baythroid H and Responsar. It is used extensively indoors, outdoors and in animal farm buildings as well as a residual spray and thermal fog for the control of flying pests like flies and mosquitoes and crawling pests such as cockroaches, fleas, bedbugs, ticks,

silverfish and beetles.

The present study was conducted to examine the neurotoxicity of cyfluthrin to mammals by measuring the effect of repeated intraperitoneal adminstration at three different sublethal dose levels on the concentrations of DA, NE and E in the olfactory bulb (OB), hypothalamus (HYP), cerebellum (CER), medulla oblongata (MO) and thoracic (TSC) and lumber (LSC) regions of the spinal cord. These regions of the brain and spinal cord were chosen for this study because of their well known involvement in the centeral nervous system catecholaminergic pathways in mammals (Lindvall and Bjorklund, 1974; Hokfelt et al., 1976; Moore and Bloom, 1978, 1979; Fung and Barnes, 1984).

MATERIALS AND METHODS

Cylfuthrin was obtained from Bayer company and applied as commerical liquid concentrate with purity level of 50 %. It was emulsified in deionized water for the final concentrations needed.

The median intraperitoneal lethal dose (LD50) of this insecticide for male albino rats (Sprague Dawley) was determined according to Litchfield and Wilcoxon (1949) and found to be 165 mg/kg body weight.

Rats weighing 100-150 gm were divided into four groups (30 rats in each of the 1st, 2nd and 3rd groups and 5 rats in the 4th group).

Rats of the 1st group received intraperitoneal administration of cyfluthrin every other day for 18 days at the dose level of 1/4 LD50.

Rats of 2nd and 3rd groups recived a daily intraperitoneal administration of cyfluthrin for 18 days and 6 weeks at the dose levels of 1/8 LD50 and 1/50 LD50 respectively.

Five rats of the 1st and 2nd groups were sacrificed by decapitation one day after the 3rd, 6th, 9th, 12th, 15th and 18th days of treatment. Five rats of the 3rd group were decapitated one day after the 1st, 2nd, 3th, 4th, 5th and 6th weeks of treatment.

Animals of the 4th group (5rats) were used as control. They received food and water *ad libitum* and were decapitated after the completion of injection of all groups.

Following decapitation of each animal, the olfactory bulb, hypothalamus, cerebellum, medulla oblongata and known portions of the thoracic and lumber regions of the spinal cord were immediately excised, washed in ice phosphate buffered saline solution, plotted on a filter paper, weighed and homogenated in 6 ml of cold sucrose solution and used for quantitative determination of catecholamine concentrations in each of the examined tissue.

Dopamine, norepinephrine and epinephrin concentrations were determined following the method of Sourkes and Murphy (1965).

Significance of difference in catecholamine concentrations of the selected regions of brain and spinal cord in control versus treated animals was tested using the Student "t" test (Parker, 1979).

RESULTS

A- SIGNS OF TOXICITY AND BEHAVIOURAL CHANGES

Observations of animals treated intraperitoneally with any of the three applied dose levels of cyfluthrin revealed that they gradually developed similar but delayed signs of toxicity and behavioural changes involving , transient skin paresthesia , facial tremor extending gradually to the whole body , bunched back posture , motor incoordination (splayed hind legs) , choreoathetotic writhing and profuse salivation . Clonic and tonic seizures were usually observed in terminal stages. These changes were gradually increased over time and become more violent , thereafter, the symptoms diminished , but in some cases led to death.

The onset and duration of these changes were found to be time and dose dependent, where , symptoms appeared at 1 , 2 and 4 hours and lasted for 8 , 4 and 2 hours after the insecticide administration at the dose levels of 1/4 , 1/8 and 1/50 LD 50 respectively .

II- EFFECT OF 1/4 LD50 DOSE LEVEL OF CYFLUTHRIN ON DA,NE AND E CONCENTRATIONS

Data presented in table (1) demonstrate a general but time and regional dependent increase of DA level in the studied brain and spinal cord regions in rats treated intraperitoneally every other day with cyfluthrin at the dose level of 1/4 LD50. The maximum increase was observed after treating animals for 6 days in OB, HYP, CER and

LSC and for 18 days in MO and TSC. The minimum levels of increase were recorded after treating rats for 3 days in OB, MO and TSC, for 12 days in HYP, and for 15 days in CER and LSC.

Table (2) shows that NE level was elevated markedly in all studied brain and spinal cord regions in rats treated intraperitoneally every other day with 1/4 LD50 dose level of cyfluthrin. The higest elevation levels were observed after 6 days of treatment in all regions. Whereas, the lowest levels of elevation were observed after 15 days of treatment in OB and LSC and after 18 days in HYP, CER, MO and TSC.

In table (3), it is demonstrated that the 1/4 LD50 dose level of cyfluthrin induced general increase in the E concentration that was maximized after 6 days of treatment in all studied brain and spinal cord regions, and was minimized after 18 days of treatment in OB, HYP, MO and TSC and after 15 and 3 days of treatment in CER and LSC respectively.

III- EFFECT OF 1/8 LD50 DOSE LEVEL OF CYFLUTHRIN ON DA, NE AND E CONCENTRATIONS

Table (4) shows that daily administration of cyfluthrin at the dose level of 1/8 LD50 into rats increased DA concentration in all studied brain and spinal cord regions. The maximum increase was recorded after 6 days treatment in OB and after 18 days in HYP, CER, MO, TSC and LSC. The minimum increase in DA concentration was at the lowest levels after 3 days of treatment in all studied regions.

Data presented in table (5) demonstrate that daily administration of 1/8 LD50 dose level of the cyfluthrin, induced a general increase of NE levels in the examined brain and spinal cord regions. This increase was at its higest level after 12 days of treatment in OB, HYP, MO and TSC and after 6 and 15 days of treatment in CER and LSC respectively. The minimum level of increase was observed after 3 and 15 days of treatment in OB and HYP respectively and following 18 treatment days in the remaining studied regions of brain and spinal cord.

In table (6), it is shown that intraperitoneal administration of cyfluthrin at the dose level of 1/8 LD50 caused a general but time and regional dependent increase of E concentration. The highest levels of increase were observed after 6 days of treatment in OB, TSC and LSC, and after 12 days in MO and following 3 and 12 days of treatment in HYP and CER respectively. The minimum increase level was recorded after 15 days of treatment in OB, MO, TSC and LSC, but was recorded after 9 and 18 days of treatment in HYP and CER.

VI- EFFECT OF 1/50 LD 50 DOSE LEVEL OF CYFLUTHRIN ON DA , NE AND E CONCENTRATIONS

Table (7) shows a general increase of DA level in all studied brain and spinal cord regions as a result of daily intraperitoneal administration of cyfluthrin at the dose level of 1/50 LD50 for 6 weeks. The increase was maximized after 3 and 2 weeks of treatment in OB and MO respectively, and after 5 weeks in HYP, CER, TSC and LSC. Minimum levels of increase were recorded after one week treatment in all studied regions of the brain and spinal cord.

Data presented in table (8) demonstrate a general increase in NE concentration of brain and spinal cord regions in rats treated intraperitoneally with cyfluthrin at the dose level of 1/50 LD50 for 6 weeks The maximum level of this increase was obtained after two treatment weeks in OB, HYP ,CER , MO and LSC, and after 4 weeks of treatment in TSC. However, the minimum levels of increase were observed after 6 weeks of treatment in all studied regions of brain and spinal cord.

Table (9) shows that daily intraperitoneal administration of cyfluthrin at the dose level of 1/50 LD50 for six weeks induced a general increase of E concentration, that was maximized after 4 weeks of treatment in OB, HYP, TSC and LSC, and after 6 weeks of treatment in CER and MO. Whereas, the minimum level of increase was recorded after one week of treatment in MO ,CER and LSC and after 5 weeks in OB, and after 6 weeks in HYP, and TSC .

DISCUSSION

In this study, it was indicated that exposure of rats to intraperitoneal sublethal doses of the synthetic pyrethroid cyfluthrin produced delayed toxicity symptoms and behavioural changes representing the typical CS syndromes produced by α-cyano pyrethroids . Similar

symptoms were previously recorded in rats given deltamethrin intravenouslly (Cremer and Seville , 1982) , or orally (Husain et al . , 1996) .

The time of onset and duration of the present toxicity symptoms was dose dependent , the lower the dose , the more delayed the onset and the shorter the duration of these symptoms .

It has been previously reported that the time of onset and duration of signs of pyrethroid toxicity was dependent to a large extent on the structure of the applied compound (Verschoyle and Aldridge , 1980) . Furthermore , it has been shown that agents eliciting the CS syndrome had greater access to the CNS than those producing T syndrome (Marci et al . , 1982) . Thus , it seems that there is a threshold concentration in the CNS for each pyrethroid that should be reached before a particular sign of toxicity occured , which would persist for as long as the pyrethroid concentration is maintained .

Separate daily intraperitoneal administration of cyfluthrin at the dose levels of 1/4 LD50 and 1/8 LD50 for 3, 6, 9, 12, 15 and 18 days, and at the dose level of 1/50 LD50 for 1, 2, 3, 4, 5 and 6 weeks into male rats, produced a general increase of DA, NE and E concentrations in all examined regions of brain and spinal cord in a dose, time and regional dependent manner.

These results coincide with previous observations obtained from studies on catecholamine levels in brain of animals treated with different insecticides including the organophosphates leptophose in mice (Aldous et al., 1982), nuvacron in rats (Gupta et al., 1984); the carbamate furadan in rats (Gupta et al., 1984); the organochlorine lindane in rats (Sunol et al., 1988 a) and the pyrethroids fenvalerate and cypermethrin in neonatal rats (Malaviya et al., 1993).

Despite the absence of any explanation provided by the present data concerning the mechanism by which cyfluthrin induced the observed elevation of brain and spinal cord catecholamine levels, a number of suggested possibilies could still be discussed.

It is possible that cyfluthrin might have induced its effect through an interaction with catecholaminergic synthesizing or metabolizing enzyme activities. Enzymes involved in the synthesis of DA, NE and E are known to include tyrosine hydroxylase, dopa decarboxylase, dopamine-β-hydroxylase and phenylethanolamine-N-methyl transferase (Bowman and Rand, 1980). It has been documented that changes in the rate of synthesis, levels or activity of these enzymes would interfere with catecholamine biosynthesis processes (Cooper et al., 1982). The decrease of DA level previously observed in the mesencephalon of rats treated with the organochlorine lindane was suggested to indicate a direct effect of lindane on the cell bodies or dopaminergic pathways by way of an increased synthesis of DA (Sunol et al., 1988 a, b).

A possible cyfluthrin-induced inhibition in the activity of the metabolizing enzyme monoamine oxidase (MAO) could be suggested to account for the present increase of catecholamine levels. This enzyme occurs in the mitochondria of the central neurones utilizing DA, NE and E and functions to catalyze the oxidative deamination of these neurotransmitters. It has been reported that, inhibition of MAO activity results in an increase in the catecholamines content of the mammalian brain (Bowman and Rand, 1980). Moreover, in a more recent study, it has been shown that oral treatment of female rats with the pyrethroid insecticide fenvalerate during lactation period caused a marked decrease in the brain MAO activity of neonatal rats (Malaviya et al., 1993).

Another suggested possibility for the present increase in catecholamine levels is that, it might have been a result of a possible cyfluthrin - induced inhibition of DA, NE and E releasing processes from central catecholaminergic axonal terminals. Two postulated mechanisms could be discussed for a possible insecticide-induced catecholamine release inhibition hypothesis.

First, it is possible that this suggested release inhibition might have been resulted from cyfluthrin-induced modifications in the electrical activity of presynaptic membranes of catecholaminergic axonal terminals. It has been previously reported that sodium channels are the primary target site of pyrethroids in nerve membranes (Vijverberg and Van-den Berken, 1990). This was a confirmatory report for earlier observations that α-cyano pyrethroids (Type II) produce a long delay in sodium channel inactivation, leading to a persistent depolarization of the axonal membrane without repetitive discharge, followed by a reduction in the size of any subsequent action potential and an eventual failure of axonal conduction (Narahashi, 1985). In the mammalian central nervous

system, the membrane depolarization - induced blockade of conduction in the axonal terminals has been postulated to underlie the process of presynaptic inhibition which is characterized by a marked diminution of neurotransmitter release (Schmidt, 1971).

Second, the possible inhibition of catecholamine release could be suggested to occur as a consequence process to the action of the insecticide - induced excess released or accumulated acetylcholine or catecholamines on muscarinic or adrenergic receptors respectively located in the presynaptic membranes of central catecholaminergic axonal terminals.

The possible role of high synaptic acetylcholine level in the suggested insecticide-induced catecholamine release inhibition is supported by previous findings that administration of high dose level of acetycholine (0.1μmol / L and above) into experimental animals inhibited the release of NE from stimulated adrenergic nerve terminals, in various tissues (Bowman and Rand, 1980). In addition it has been shown that administration of the pyrethroids fenvalerate and cypermethrin by gavage into pregnant and nursing female rats during gestation and lactation periods induced a significant decrease in brain acetylcholinesterase (AchE) activity simultaneously with a significant increase in brain DA level and an increase in muscarinic receptors of striatal membrane in neonatal rats (Malaviya et al., 1993). Moreover, the present authors have recently reported that intraperitoneal administration of similar dose levels of cyfluthrin into male rats produced a general inhibition of AChE activity in the same brain and spinal cord regions studied in the present investigation (Ahmed et al., 1995). Inhibition of AChE activity is well known to cause synaptic accumlation of acetylcholine (Taylor, 1990).

The suggestion that high level of endogenously released catecholamines could inhibit its own additional release is supported by the previously established concept that high local synaptic concentration of catecholamine neurotransmitters have an inhibitory feed-back effect on further transmitter release by interacting with presynaptic autoreceptors (Bowman and Rand, 1980; Cooper et al., 1982).

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Table 1 : Effect of intraperitoneal administration of cyfluthrin every other day at the dose level of ¼ LD50 for 3, 6, 9, 12, 15 and 18 days on dopamine concentrations (µg/g fresh tissue) in selected brain and spinal cord regions of male albino rats. Each point represents the mean of five separate experiments.

Brain and spinal cord regions	Control	Time (days) before decapitation of treated animals					
		3	6	9	12	15	18
Olfactory Bulb	0.66 ± 0.08	1.54 ± 0.28 P < 0.05	3.62 ± 0.28 P < 0.01	2.94 ± 0.54 P < 0.01	1.86 ± 0.27 P < 0.01	2.81 ± 0.16 P < 0.001	3.52 ± 0.75 P < 0.001
Hypothalamus	0.12 ± 0.01	1.09 ± 0.06 P < 0.001	2.37 ± 0.23 P < 0.001	1.97 ± 0.33 P < 0.001	0.88 ± 0.11 P < 0.001	1.76 ± 0.26 P < 0.001	2.06 ± 0.14 P < 0.001
Cerebellum	0.79 ± 0.09	3.01 ± 0.33 P < 0.001	5.97 ± 0.48 P < 0.001	4.25 ± 1.00 P < 0.01	2.67 ± 0.41 P < 0.01	1.55 ± 0.22 P < 0.05	2.03 ± 0.16 P < 0.001
Medulla Oblongata	0.38 ± 0.04	2.49 ± 0.37 P < 0.001	5.67 ± 0.94 P < 0.001	4.60 ± 0.57 P < 0.001	3.66 ± 0.43 P < 0.001	4.99 ± 0.39 P < 0.001	7.19 ± 0.41 P < 0.001
Thoracic Spinal Cord	2.17 ± 0.18	2.61 ± 0.34 P > 0.05	3.97 ± 0.59 P < 0.01	3.14 ± 0.30 P < 0.05	2.95 ± 0.38 P > 0.05	4.73 ± 0.37 P < 0.001	6.29 ± 0.36 P < 0.001
Lumbar Spinal Cord	1.28 ± 0.08	4.66 ± 0.61 P < 0.001	6.11 ± 0.62 P < 0.001	5.12 ± 0.63 P < 0.001	3.67 ± 0.46 P < 0.001	1.45 ± 0.24 P > 0.05	1.76 ± 0.37 P > 0.05

P > 0.05 Non-Significant.

P < 0.05 Significant.

P < 0.01 Highly Significant.

P < 0.001 More Highly Significant.

Table 2 : Effect of intraperitoneal administration of cyfluthrin every other day at the dose level of ¼ LD50 for 3, 6, 9, 12, 15, and 18 days on norepinephrine concentrations (µg/g fresh tissue) in selected brain and spinal cord regions of male albino rats. Each point represents the mean of five separate experiments.

Brain and spinal cord regions	Control	Time (days) before decapitation of treated animals					
		3	6	9	12	15	18
Olfactory Bulb	11.58 ± 1.41	76.14 ± 0.98 P < 0.001	81.41 ± 1.10 P < 0.001	50.61 ± 0.88 P < 0.001	33.22 ± 0.29 P < 0.01	13.03 ± 0.51 P > 0.05	19.54 ± 0.79 P < 0.05
Hypothalamus	10.28 ± 0.48	42.96 ± 3.91 P < 0.001	59.93 ± 4.91 P < 0.001	38.42 ± 4.96 P < 0.001	20.13 ± 3.99 P < 0.05	16.66 ± 0.57 P < 0.01	12.55 ± 0.67 P > 0.05
Cerebellum	29.46 ± 1.85	142.68±4.72 P < 0.001	175.34±7.80 P < 0.001	97.42 ± 6.73 P < 0.001	49.95 ± 4.22 P < 0.001	39.62 ± 1.87 P < 0.001	35.31 ± 1.11 P > 0.05
Medulla Oblongata	21.11 ± 2.04	175.58±3.29 P < 0.001	200.41±2.08 P < 0.001	153.67±2.17 P < 0.001	92.42 ± 5.04 P < 0.001	50.50 ± 1.75 P < 0.001	23.11 ± 2.75 P > 0.05
Thoracic Spinal Cord	21.37 ± 1.37	160.26±4.21 P < 0.001	198.14±14.91 P < 0.01	115.64±8.71 P < 0.001	61.28±10.11 P > 0.01	25.44 ± 1.13 P < 0.05	22.09 ± 2.87 P > 0.05
Lumbar Spinal Cord	21.95 ± 0.67	86.43 ± 0.91 P < 0.001	105.76±2.09 P < 0.001	77.32 ± 0.87 P < 0.001	47.11 ± 1.00 P < 0.001	22.77 ± 0.76 P > 0.05	29.57 ± 1.00 P < 0.05

P > 0.05 Non-Significant.

P < 0.05 Significant.

P < 0.01 Highly Significant.

P < 0.001 More Highly Significant.

Table 3 : Effect of intraperitoneal administration of cyfluthrin every other day at the dose level of ¼ LD50 for 3, 6, 9, 12, 15, and 18 days on epinephrine concentrations (µg/g fresh tissue) in selected brain and spinal cord regions of male albino rats. Each point represents the mean of five separate experiments.

Brain and spinal cord regions	Control	Time (days) before decapitation of treated animals					
		3	6	9	12	15	18
Olfactory Bulb	2.52 ± 0.21	20.81 ± 0.98 P < 0.001	37.69 ± 3.91 P < 0.001	24.62 ± 3.96 P < 0.001	16.26 ± 1.87 P < 0.001	6.56 ± 1.28 P < 0.05	2.67 ± 0.12 P > 0.05
Hypothalamus	1.55 ± 0.16	7.71 ± 0.30 P < 0.001	9.70 ± 0.74 P < 0.001	6.26 ± 0.70 P < 0.001	4.80 ± 0.98 P < 0.01	2.81 ± 0.12 P < 0.001	2.20 ± 0.03 P < 0.01
Cerebellum	8.54 ± 0.88	33.74 ± 2.56 P < 0.001	45.63 ± 5.05 P < 0.001	38.00 ± 4.14 P < 0.001	19.35 ± 3.44 P < 0.01	11.48 ± 0.99 P > 0.05	12.50 ± 0.17 P < 0.05
Medulla Oblongata	9.56 ± 0.55	36.05 ± 0.97 P < 0.001	47.81 ± 6.06 P < 0.001	41.46 ± 2.28 P < 0.001	21.85 ± 2.59 P < 0.001	16.33 ± 0.48 P < 0.01	14.66 ± 0.45 P < 0.05
Thoracic Spinal Cord	15.69 ± 1.01	35.17 ± 2.47 P < 0.001	43.62 ± 4.45 P < 0.001	32.76 ± 1.87 P < 0.001	26.79 ± 2.17 P < 0.01	18.92 ± 0.68 P < 0.01	16.23 ± 0.43 P > 0.05
Lumbar Spinal Cord	8.62 ± 0.58	13.76 ± 0.99 P < 0.05	29.96 ± 3.57 P < 0.001	21.50 ± 3.23 P < 0.01	17.12 ±2.62 P < 0.01	16.94 ± 1.41 P < 0.01	18.34 ± 1.99 P < 0.01

P > 0.05 Non-Significant.

P < 0.05 Significant.

P < 0.01 Highly Significant.

P < 0.001 More Highly Significant.

Table 4 : Effect of daily intraperitoneal administration of cyfluthrin at the dose level of 1/8 LD50 for 3, 6, 9, 12, 15, and 18 days on dopamine concentrations (μg/g fresh tissue) in selected brain and spinal cord regions of male albino rats. Each point represents the mean of five separate experiments.

Brain and spinal cord regions	Control	Time (days) before decapitation of treated animals					
		3	6	9	12	15	18
Olfactory Bulb	0.66 ± 0.08	1.20 ± 0.06 P < 0.01	4.02 ± 0.73 P < 0.01	2.84 ± 0.55 P < 0.01	2.05 ± 0.39 P < 0.01	1.61 ± 0.20 P < 0.01	3.31 ± 0.45 P < 0.001
Hypothalamus	0.12 ± 0.01	0.45 ± 0.05 P < 0.01	1.07 ± 0.21 P < 0.01	0.88 ± 0.30 P < 0.05	1.83 ± 0.28 P < 0.001	3.00 ± 0.30 P < 0.001	4.25 ± 0.65 P < 0.001
Cerebellum	0.79 ± 0.09	0.98 ± 0.11 P > 0.05	2.49 ± 0.24 P < 0.001	1.56 ± 0.21 P < 0.01	2.87 ± 0.36 P < 0.001	3.07 ± 0.27 P < 0.001	7.36 ± 1.36 P < 0.001
Medulla Oblongata	0.38 ± 0.04	2.30 ± 0.36 P < 0.01	5.65 ± 0.60 P < 0.001	3.88 ± 0.58 P < 0.001	2.42 ± 0.41 P < 0.001	2.87 ± 0.56 P < 0.01	10.27 ± 1.10 P < 0.001
Thoracic Spinal Cord	2.17 ± 0.18	2.72 ± 0.18 P > 0.05	5.43 ± 0.80 P < 0.01	3.20 ± 0.50 P < 0.05	6.06 ± 1.15 P < 0.01	7.90 ± 0.50 P < 0.001	11.72 ± 0.24 P < 0.001
Lumbar Spinal Cord	1.28 ± 0.08	1.76 ± 0.24 P > 0.05	3.56 ± 0.38 P < 0.001	2.85 ± 0.50 P < 0.05	4.05 ± 0.41 P < 0.001	5.22 ± 1.44 P <0.05	5.44 ± 0.65 P< 0.001

P > 0.05 Non-Significant.

P < 0.05 Significant.

P < 0.01 Highly Significant.

P < 0.001 More Highly Significant.

Table 5 : Effect of daily intraperitoneal administration of cyfluthrin at the dose level of 1/8 LD50 for 3, 6, 9, 12, 15, and 18 days on norepinephrine concentrations (µg/g fresh tissue) in selected brain and spinal cord regions of male albino rats. Each point represents the mean of five separate experiments.

Brain and spinal cord regions	Control	Time (days) before decapitation of treated animals					
		3	6	9	12	15	18
Olfactory Bulb	11.58 ± 1.41	11.73 ± 0.83 P > 0.05	12.73 ± 1.48 P > 0.05	18.82 ±1.72 P < 0.05	26.05 ± 2.80 P < 0.001	13.40 ± 0.89 P < 0.05	13.70 ± 0.43 P < 0.05
Hypothalamus	10.28 ± 0.48	14.49 ± 0.64 P < 0.01	16.43 ± 0.88 P < 0.01	14.83 ± 0.31 P < 0.01	16.77 ± 0.67 P < 0.01	10.36 ± 1.56 P >0.05	12.24 ± 0.24 P > 0.05
Cerebellum	29.46 ± 1.85	38.53 ± 1.28 P < 0.05	41.58 ±1.54 P < 0.01	34.88 ± 1.4 P > 0.05	33.82 ± 3.28 P > 0.05	34.59 ± 2.44 P > 0.05	31.93 ± 1.04 P > 0.05
Medulla Oblongata	21.11 ± 2.04	28.16 ± 1.85 P < 0.05	33.18 ± 2.61 P < 0.01	40.81 ± 3.47 P < 0.001	51.76 ± 4.02 P < 0.001	35.72 ±3.35 P < 0.05	21.89 ± 2.34 P > 0.05
Thoracic Spinal Cord	21.37 ± 1.37	30.77 ± 2.55 P < 0.05	41.61 ± 2.28 P < 0.001	37.47 ± 2.74 P < 0.001	55.56 ± 3.90 P < 0.001	38.85 ± 0.99 P < 0.001	23.11 ± 0.76 P > 0.05
Lumbar Spinal Cord	21.95 ± 0.67	29.02 ± 0.68 P < 0.05	33.56 ± 3.11 P < 0.001	23.79 ± 1.04 P > 0.05	27.16 ± 2.47 P < 0.01	37.91 ± 2.55 P < 0.001	23.02 ± 1.24 P > 0.05

P > 0.05 Non-Significant.

P < 0.05 Significant.

P < 0.01 Highly Significant.

P < 0.001 More Highly Significant.

Table 6 : Effect of daily intraperitoneal administration of cyfluthrin at the dose level of 1/8 LD50 for 3, 6, 9, 12, 15, and on epinephrine concentrations (µg/g fresh tissue) in selected brain and spinal cord regions of male albino rats. Each point represents the mean of five separate experiments.

Brain and spinal cord regions	Control	Time (days) before decapitation of treated animals					
		3	6	9	12	15	18
Olfactory Bulb	2.52 ± 0.21	21.80 ± 2.32 P < 0.001	29.93 ± 1.55 P < 0.001	14.09 ± 1.27 P < 0.001	21.46 ± 2.58 P < 0.001	4.95 ± 0.45 P < 0.001	10.03±0.90 P > 0.001
Hypothalamus	1.55 ± 0.16	8.46 ± 0.59 P < 0.001	4.55 ± 0.57 P < 0.001	2.54 ± 0.18 P < 0.001	6.68 ± 0.66 P < 0.001	2.80 ± 1.11 P < 0.05	4.60 ± 1.27 P < 0.01
Cerebellum	8.54 ± 0.88	21.41 ± 1.37 P < 0.001	26.63 ± 1.17 P < 0.001	18.08 ± 1.69 P < 0.01	31.61 ±2.36 P < 0.001	17.14 ± 0.54 P < 0.001	14.71 ± 0.41 P < 0.001
Medulla Oblongata	9.56 ± 0.55	27.02 ± 1.68 P < 0.001	33.81 ± 3.69 P < 0.001	29.71 ± 3.41 P < 0.001	43.32 ± 5.91 P < 0.001	16.55±0.41 P < 0.01	19.19 ± 1.44 P < 0.001
Thoracic Spinal Cord	15.69 ± 1.01	33.11 ± 2.35 P < 0.001	46.27 ± 3.58 P < 0.001	36.40 ± 2.71 P < 0.001	24.59 ± 2.33 P < 0.05	15.75 ± 3.39 P > 0.05	23.84 ± 2.40 P < 0.01
Lumbar Spinal Cord	8.62 ± 0.58	21.30 ± 0.94 P < 0.001	25.38 ± 1.88 P < 0.001	15.86 ± 1.41 P < 0.01	21.35 ±1.85 P < 0.001	14.12 ± 0.37 P < 0.01	19.66 ± 2.33 P < 0.001

P > 0.05 Non-Significant.

P < 0.05 Significant.

P < 0.01 Highly Significant.

P < 0.001 More Highly Significant.

Table 7 : Effect of daily intraperitoneal administration of cyfluthrin at the dose level of 1/50 LD50 for 1, 2, 3, 4, 5 and 6 weeks on dopamine concentrations (μg/g fresh tissue) in selected brain and spinal cord regions of male albino rats. Each point represents the mean of five separate experiments.

Brain and spinal cord regions	Control	Time (weeks) before decapitation of treated animals					
		1	2	3	4	5	6
Olfactory Bulb	0.66 ± 0.08	2.81 ± 0.95 P < 0.001	4.72 ± 1.02 P < 0.001	5.13 ± 1.13 P < 0.001	3.56 ± 1.35 P < 0.001	2.97 ± 1.84 P < 0.001	4.10 ± 0.15 P < 0.001
Hypothalamus	0.12 ± 0.01	0.62 ± 0.07 P < 0.001	1.14 ± 0.12 P < 0.001	0.99 ± 0.31 P < 0.001	1.25 ± 0.56 P < 0.001	2.93 ± 0.74 P < 0.001	1.85 ± 0.56 P < 0.001
Cerebellum	0.79 ± 0.09	0.97 ± 0.03 P > 0.05	2.56 ± 0.35 P < 0.001	1.87 ± 0.55 P < 0.01	3.11 ± 0.46 P < 0.001	3.56 ± 0.81 P < 0.001	2.64 ± 0.73 P < 0.001
Medulla Oblongata	0.38 ± 0.04	1.26 ± 0.08 P < 0.001	3.36 ± 0.42 P < 0.001	2.72 ± 0.34 P < 0.001	2.55 ± 0.29 P < 0.001	3.09 ± 0.96 P < 0.001	1.97 ± 0.83 P < 0.001
Thoracic Spinal Cord	2.17 ± 0.18	2.88 ± 0.33 P > 0.05	3.62 ± 0.57 P < 0.01	2.94 ± 0.40 P > 0.05	3.90 ± 0.40 P < 0.01	4.12 ± 0.64 P < 0.001	3.54 ± 0.75 P < 0.01
Lumbar Spinal Cord	1.28 ± 0.08	1.73 ± 0.12 P > 0.05	2.95 ± 0.33 P < 0.001	2.19 ± 0.19 P < 0.01	3.27 ± 0.93 P < 0.001	3.94 ± 0.75 P < 0.001	2.65 ± 0.57 P < 0.001

P > 0.05 Non-Significant.

P < 0.05 Significant.

P < 0.01 Highly Significant.

P < 0.001 More Highly Significant.

Table 8 : Effect of daily intraperitoneal administration of cyfluthrin at the dose level of 1/50 LD50 for 1, 2, 3, 4, 5 and 6 weeks on norepinephrine concentrations (µg/g fresh tissue) in selected brain and spinal cord regions of male albino rats. Each point represents the mean of five separate experiments.

Brain and spinal cord regions	Control	Time (weeks) before decapitation of treated animals					
		1	2	3	4	5	6
Olfactory Bulb	11.58 ± 1.41	69.82 ± 8.67 P < 0.001	75.47 ± 1.84 P < 0.001	64.74 ± 7.38 P < 0.001	46.79 ± 6.59 P < 0.001	62.56 ± 9.96 P < 0.01	29.91 ± 1.36 P < 0.05
Hypothalamus	10.28 ± 0.48	25.92 ± 1.74 P < 0.001	30.41 ± 1.02 P < 0.001	22.21 ± 2.98 P < 0.01	21.02 ± 1.99 P < 0.01	13.00 ± 1.76 P > 0.05	12.53 ± 0.31 P > 0.05
Cerebellum	29.46 ± 1.85	90.24 ± 4.44 P < 0.001	120.34±4.93 P < 0.001	106.94±6.86 P < 0.001	45.77 ± 6.89 P < 0.05	94.79 ± 15.1 P < 0.01	31.51 ± 4.96 P > 0.05
Medulla Oblongata	21.11 ± 2.04	153.20±13.17 P < 0.001	176.25±7.35 P < 0.001	104.70±2.74 P < 0.01	148.32±9.79 P < 0.001	74.54 ± 6.85 P < 0.001	29.67 ± 4.05 P < 0.05
Thoracic Spinal Cord	21.37 ± 1.37	150.57±8.77 P < 0.001	178.95±5.18 P < 0.001	97.35 ± 6.02 P < 0.001	199.50±3.70 P < 0.001	40.72 ± 2.54 P < 0.001	21.94 ± 3.93 P > 0.05
Lumbar Spinal Cord	21.95 ± 0.67	119.88±5.10 P < 0.001	139.15±6.11 P < 0.001	86.47±12.44 P < 0.001	88.12 ± 5.87 P < 0.001	84.11 ± 5.02 P < 0.001	23.20 ± 2.95 P > 0.05

P > 0.05 Non-Significant.

P < 0.05 Significant.

P < 0.01 Highly Significant.

P < 0.001 More Highly Significant.

Table 9 : Effect of daily intraperitoneal administration of cyfluthrin at the dose level of 1/50 LD50 for 1, 2, 3, 4, 5 and 6 weeks on epinephrine concentrations (µg/g fresh tissue) in selected brain and spinal cord regions of male albino rats. Each point represents the mean of five separate experiments.

Brain and spinal cord regions	Control	Time (weeks) before decapitation of treated animals					
		1	2	3	4	5	6
Olfactory Bulb	2.52 ± 0.21	12.19 ± 0.94 P < 0.001	27.31 ± 2.16 P < 0.001	16.46 ± 4.95 P < 0.01	39.71±14.86 P < 0.05	5.61 ± 0.36 P < 0.01	10.37±1.26 P > 0.001
Hypothalamus	1.55 ± 0.16	4.94 ± 0.50 P < 0.001	6.24 ± 0.84 P < 0.001	4.06 ± 0.79 P < 0.05	7.18 ± 1.44 P < 0.001	4.59 ± 0.31 P < 0.001	3.04 ± 0.11 P < 0.01
Cerebellum	8.54 ± 0.88	16.36 ± 1.64 P < 0.01	35.29 ± 3.62 P < 0.001	25.05 ± 6.56 P < 0.05	21.27 ± 5.78 P < 0.05	27.24 ± 1.89 P < 0.001	40.03 ± 4.35 P < 0.001
Medulla Oblongata	9.56 ± 0.55	18.33 ± 1.76 P < 0.01	40.02 ± 3.15 P < 0.001	33.86±13.87 P < 0.05	54.57 ± 3.83 P < 0.001	29.45 ± 2.02 P < 0.001	79.62 ± 7.94 P < 0.001
Thoracic Spinal Cord	15.69 ± 1.01	29.10 ± 1.26 P < 0.001	35.61± 2.42 P < 0.001	30.71 ± 3.60 P < 0.01	52.52 ± 7.48 P < 0.001	23.14 ± 1.31 P < 0.001	20.68 ± 3.10 P > 0.05
Lumbar Spinal Cord	8.62 ± 0.58	14.10 ± 0.50 P < 0.001	23.07 ± 1.57 P < 0.001	18.98 ± 3.13 P < 0.01	31.63 ± 4 .92 P < 0.001	19.26 ± 3.06 P < 0.01	29.11 ± 2.34 P < 0.001

P > 0.05 Non-Significant.

P < 0.05 Significant.

P < 0.01 Highly Significant.

P < 0.001 More Highly Significant.