REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Cellular Mechanism involved in cypermethrin induced neurotoxicity

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Abstract

Cypermethrin (CYP): Is a class II synthetic pyrethroid that can cause in general irritation, itching at skin and eyes, burning sensation and loss of bladder control through ingestion or directly through dermal absorption exerts**.** It causes neurotoxicity passing through blood brain barrier in the central nervous system & induces motor deficits. Cypermethrin does not only causing neurotoxicity on central nervous system, but it's also affecting the peripheral nervous system.The inhibtory effect on the γ-aminobutyric acid (GABA) receptor, causing excitability and convulsions by decreasing the calcium uptake by nerves**,** suppression in immune system function in rats, it showed decrease in the numbers of Natural killer NK cells and increase in serum immunoglobulins (Igs) and causes early embryonic deaths, damage in genetic material, disrupts the sexual behavior and estrous cycle disruption**.** Exposure to low dose of CYP didn't produce any alternation in GPx, CAT, and SOD activities**.** Generates proinflammatory cytokines as interleukins (IL) and tumor necrosis factor alpha (TNF-α) induced by activation of microglia and astrocytes caused by cypermethrin, this activation led to increase the level of TNF-α and IL-1β**.**

Keywords: Cypermethrin, GABA, GPx, TNF-α , IL-1β.

1. Introduction

Cypermethrin is a synthetic pyrethroid pesticide which is a organic pesticide. CYP is commonly used pesticide in agriculture because it is a mixture of all eight possible chiral isomers to control ectoparasites that infest cattle, sheep, and poultry **(Meyling *et al.*, 2018).** Cypermethrin is result from condensation between 3-(2,2-dichlorovinyl)-2,2-dimethylcycloprpanecarboxlic acid and the alcoholic hydroxy group of hydro(3-phenoxyphenyl)acetonitile form a carboxlic ester with IUPAC name [cyano-(3-phenoxyphenyl)methyl]3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate (Fig.1).

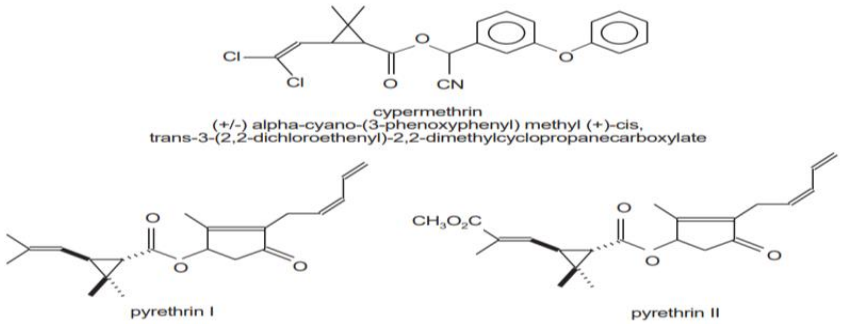

Figure (1): Cypermethrin and related naturally-occurring insecticidal chemicals (Cox, 1996).

Mode of action of cypermethrin:

All synthetic pyrethroids kill pests by interrupting the normal function of the nervous system of the pests. CYP has the same way of action like all pyrethiods **(Soderlund, 2010)**.

The normal function of nervous system in all animals and inscects is transduction of nerve impulse. This is done by exchange in sodium and potassium ions through sodium-potassium gate **(Lodish *et al.*, 2000)**.

CYP delays the closure of sodium-potasium gate which allows the flow of sodium resulting in spelly the generation of multiple nerve impulses instead of the usual single one. Also, CYP has an inhibtory effect on the γ-aminobutyric acid receptor, causing excitability and convulsions by decreasing the calcium uptake by nerves. It inhibits monoamine oxidase and indirect affects adenosine triphosphatase that is involved in the cellular energy production, transport of metal atoms, and muscle contractions **(Narahashi, 2010)**.

General effects of cypermethrin:

CYP can cause irritation, itching at skin and eyes, burning sensation and loss of bladder control through ingestion or directly through dermal absorption. Nervous and muscular system are the major parts which are affected mainly by intoxication with CYP and other synthetic pyrethroids **(Rehman *et al.*, 2014)**.

Effect of cypermethrin on human and expermintal animals:

Medical reports have documented that exposure of human to CYP showed facial burning, tingling, headache, nausea, fatigue and loss of bladder control. Exposure to higher dose leads to muscle twitching, drowsiness, coma, and seizures. Expermintal data on laboratory animals has reported that exposure to CYP showed pawing, burrowing, salivation, tremors, writhing, and seizures **(Alwan, 2015).**

Effect of cypermethrin on the immune system:

Previous studies showed that suppression in immune system function in both rats and rabbits treated with CYP **(Wang *et al.*, 2017; Ambwani *et al.*, 2018)**. **Aroonvilairat *et al.*,(2018)** reported that dermal exposure to CYP showed decrease in the numbers of NK cells and increase in serum immunoglobulins (Igs). Earlier studies has reported that CYP decreases both humoral and cellular immune responses in rats and rabbits **(Allam *et al.*, 2016; Iteire *et al.*, 2017)**.

Effect of cypermethrin on reproduction:

Exposure to cypermethrin can effect pregnant experimental animals and their offspring. Several studies has showed that exposure of pregnant female to CYP causes early embryonic deaths, disrupts the sexual behavior and estrous cycle disruption. It adversely affects the progesterone production in bovines **(Gill *et al.*, 2011; Sangha *et al.*, 2013; Sallam *et al.*, 2015)**. Also, male reproductive system is affected by CYP. Treatment with CYP in rats caused decreases in the ejaculate volume, sperm concentration, sperm motility, semen initial fructose and plasma testosterone **(Alaa-Eldin *et al.*, 2017)**. A study has shown that inhibition of testostrone receptor in testes by CYP indicates disturbance of sex hormones **(Sharma *et al.*, 2018).**

Effect of cypermethrin on Mutagenicity:

Researches on laboratory animals have shown that CYP caused damage in genetic material. It was demonstrated that CYP induces DNA damage in vital organs such as brain, liver and kidney **(Patel *et al.*, 2006).** Injection of CYP to mice leads to abnormal chromosomes in both bone marrow and spleen **(Queiroz *et al.*, 2013)**.

Carcinogenicity of cypermethrin:

CYP is classified as human carcinogen according to EPA. A study have demonstrated that CYP cause lung tumor in mice **(Sheikh *et al.*, 2014)**.

The molecular mechanism of CYP casuing cancer may be fristly by gap junction intercellualr communication that important in cell growth and differentiation, secondly by also increased the number of altered foci **(George and Shukla, 2011).**

Other chronic effects of cypermethrin:

Long-term feeding with CYP in rats, mice and dogs showed redetion in the growth rate, increased liver weight, mild anemia, loss of appetite, incoordination, and tremors **(Baharuddin *et al.*, 2016)**. Administration of CYP orally for 21 days showed haemorrhage, congestion with focal myolysis disruption in branching structure, with loss of striations, and early necrotic changes in the myocardium of rats **(Nair *et al.*, 2011)**.

Effect of cypermethrin on nervous system:

CYP-induced neurotoxicity is indeed a matter of apprehension because the neurotoxicity effect of cypermethrin has not well-documented. Neurotoxicity of cypermethrin depend on doses, time and route of exposure that produce a variety of clinical neurotoxic effects such as tremors, paresthesia, splayed gait, paresthesia and depression **(Kumar Singh *et al.*, 2012).**

Prevoius data reported that human exposure to 10% CYP solution causes death after 3 hours **(Wang *et al.*, 2016).** CYP is causes neurotoxicity passing through blood brain barrier in the central nervous system to induce motor deficits. CYP not only cause neurotoxicity on central nervous system but also on the peripheral nervous system. A report showed preformed on CYP induced neurotoxicity in expermintal animals and reported that CYP implicated in Parkinson's disease (PD) pathogenesis **(Baltazar *et al.*, 2014).** A study performed on albino rats reproted that oral administation of CYP at (14.5 mg/kg b.w) induced neurotoixity in the cerebellum of exposed rats through disturbance in neurotransimetters such as gamma-aminobutyric acid (GABA), dopamine and acetylcholinesterase **(Elsawy *et al.*, 2017).** A report showed that CYP antagonizes GABA. A study has found that down reuglation in GABA concentration in the brain of experimental animals after expouse to a high dose of CYP **(Anantharam *et al.*, 2017)**. Administration of high dose of CYP induced the reduction in serotonin level in the frontal cortex of experimental animals **(Anshuman Singh *et al.*, 2016)**. CYP nduced decrease in acetyl- and butyryl- cholinesterase activities at high doses, however at low dose it didn't produced alteration in activities of acetyl- and butyryl-cholinesterase **(Rani *et al.*, 2017)**. A report demonstrated the adverse effect of cypermethrin includes nigrostriatal dopaminergic neurotoxicity through mitochondrial dysfunction **(Agrawal *et al.*, 2015).**

Several evidence reported that chronic exposure of rats or human to cypermethrin showed epileptic activity and behavioral anomalies **(Gómez-Giménez *et al.*, 2017; Ganie *et al.*, 2018)**.

Behavior studies on expermintal animals exposed to cypermethrin showed sequence of visible motor symptoms along with chewing, stayed limbs, increased foot splay, reduced arousal and reduced response to touch pinches **(Rashkivska *et al.*, 2017).**

Mechanism of cypermethrin induced neurotoxicity:

A study has documented that the neurotoxicity mechanism of all pyrethroids targets the sodium and magnesium channels. Few reports stated that chemically alternation of CYP so it become an axonic posion. CYP is always used with pepperoni butoxide (PBO) that acts as synergist by enhancing the effect of cyermethrin through inhibiting cytochrome P450 enzyme **(Sharma *et al.*,2018)**.

CYP induced neurotoxicity is through changing in the voltage gate of sodium channel. Voltage-gated channels composed of 1α and 2β subunits in mammalian cells. CYP causes a stable hyperexcitable state through binding to subunits of sodium channel to prevent channel from closing that cause continuous nerve stimulation **(Khan *et al.*, 2018).**

CYP also targets calcium and chloride channels that lead to distinct toxic syndromes. CYP causes inhibition of voltage-gated calcium channel (VGCC) by alters the kinetics and calcium influx that regulates the protein kinases and phosphatases. These enzymes are involved in the signal transduction pathways. CYP is a strong inhibitor of calcineurin that alters Ca^{2+} influx leading to decrese in calcium level and release of neurotransmitter **(Hernández *et al.*, 2017).**

Previous studies reported that administration of

CYP at lower concentration didn't induced any effect, however, at high concentration induced delay in phosphorylation of calcineurin and inhibition of calcium channel **(Hernández *et al.*, 2017; Meijer *et al.*, 2015; Li *et al*., 2017)**.

As CYP induced inhibition in calcium channel, it causes defect in potasium channels that regulate excitability of neurons. In constract reports demonstrated that administration of CYP at lower level cause retardation in the function of potassium channels and at higher concentrations, it inactivates the potassium current **(Cao *et al*., 2011)**.

GABA is a dominant neurotransmitter that regulates chloride channels in brain. CYP represses the voltage-gated chloride channels opening and inhibits GABA dependent uptake of chloride ions. The change in homeostasis of chloride channels leads to hyper-excitability and neurotoxicity. Inhibtion of chloride channel induced by

CYP produces minor tremors, depression, hyperesthesia, and spastic paralysis depending on the exposure dose **(Ch *et al.*, 2015).**

Burgeoning evidence has documented that cypermethrin induced neurotoxicity is closely correlated with oxidative stress. Oxidative stress resulting from reactive oxygen species (ROS) and reactive nitrogen species production. The brain is very sensitive to oxidative stress due the inhibition of enzymatic antioxidant activities caused by cypermethrin. The oxidative stress induced by cypermethrin might be dose-dependent **(Agrawal *et al.*, 2015).**

A report has documented that CYP could decrease the enzymatic antioxidant system that leads to cellular damage in lipids, protiens and DNA. Oxidative stress occurred by CYP results in cell death via apoptotic or necrotic mechanisms. DNA damage, enhanced lipid peroxidation and protein damage may occur during cell death process **(Ashish Singh *et al.*, 2016).**

Lipid peroxidation induced by oxidative stress can be measured the end products of lipid peroxidation such as malondialdehyde (MDA) and thiobarbituric acid reacting substances (TBARS). Malondialdehyde reflects the degradation of neuronal membrane. Study of CYP-induced oxidative stress in rats showed increased levels of MDA in brain tissue. More than 50% of brain weight is made up of lipids, and the membranes of nerve cells are rich in polyunsaturated fatty acids (PUFAs). Lipid peroxidation leads to loss of membrane fluidity and potential difference, thereby increasing the permeability. Many publications reported that the elevation of lipid peroxidation induced by CYP is shown in different brain regions such as hippocampus and cortex **(Kaushik, 2018; Mu *et al*., 2017)**.

Oxidative stress also targets protein as well as lipids, this can be detected by protein carbonyls (PC) resulted from oxidation of proteins. A study *in-vitro* and *in-vivo* has documented that significant increases in PC resulted by CYP administration **(Hocine *et al.*, 2016)**.

Recent study performed on rats demonstrated that exposure to high doses of CYP generate ROS represented in elevation of PC concentration in the brain tissue **(Elhalwagy *et al*., 2018)**.

It was shown indicated that enzymatic antioxidant system affected by exposure to CYP. CYP administration decreases the CAT, SOD and GPx activities in rats **(Sharma *et al.*, 2014)**.

Epidemiological studies reported that SOD has found in lower concentration in the brain with different doses of CYP **(Eraslan *et al*., 2016).**

Increase ROS due to exposure of CYP indicate that increase level of H_2O_2 with decrease CAT activity. Exposure to low dose of CYP didn't produce any alternation in GPx, CAT, and SOD activities, indicating that CYP had a dose-dependent effect on antioxidant enzymes. Recently, in a study to reveal the effect of CYP on rats, CYP led to decrease in GPx, GSH and GST activities. A recent study suggested that CYP and its metabolites, induce deformational in SOD **(MANSOUR *et al*., 2018).**

Apoptosis is a process of programmed cell death that is essential for development and tissue homeostasis **(Nagata and Tanaka, 2017)**. Previous study has been suggested that at the neuronal death caused by CYP is due to apoptosis **(Özdemir *et al.*, 2018).** It was shown documented that apoptosis in the brain is due to oxidative stress induced by cypermethrin **(Paravani *et al.*, 2018).**

Exposure to CYP at high dose or at low dose causes damage in DNA that reduces nuclear divisions. Earlier studyperformed on female rats were orally treated with cypermethrin showed that increased TBARS, and decreased GSH and the activities of the antioxidant enzymes this led to DNA damage **(Kalra, 2018).**

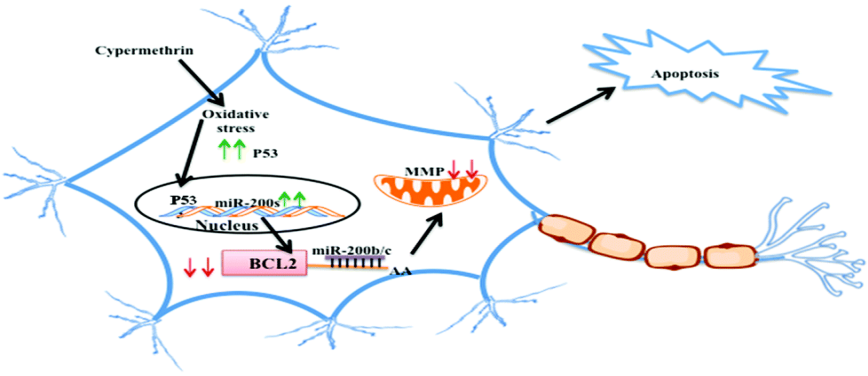

Figure (2): A schematic presentation of the role of the miR-200 family in cypermethrin-induced apoptosis of NGF differentiated PC12 cells. Double green upward arrows indicate induction, while double red arrows indicate a down-regulation in gene expression **(Pandey *et al.*, 2015)**.

The main key-players involved in neuroinflammation process induced by cypermethrin are microglia and astrocytes as demonstrated in many publications **(Gómez-Giménez *et al.*, 2017; Cankaya *et al.*, 2019)**.

Generation of proinflammatory cytokines as interleukins (IL) and tumor necrosis factor alpha (TNF-α) induced by activation of microglia and astrocytes caused by cypermethrin, this activation led to increase the level of TNF-α and IL-1β **(Vardavas et al., 2016)**.

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