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Pyrethroid exposure and neurotoxicity: a mechanistic approach

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Pyrethroids are a class of synthetic insecticides that are used widely in and around households to control the pest. Concerns about exposure to this group of pesticides are now mainly related to their neurotoxicity and nigrostriatal dopaminergic neurodegeneration seen in Parkinson's disease. The main neurotoxic mechanisms include oxidative stress, inflammation, neuronal cell loss, and mitochondrial dysfunction. The main neurodegeneration targets are ion channels. However, other receptors, enzymes, and several signalling pathways can also participate in disorders induced by pyrethroids. The aim of this review is to elucidate the main mechanisms involved in neurotoxicity caused by pyrethroids deltamethrin, permethrin, and cypermethrin. We also review common targets and pathways of Parkinson's disease therapy, including Nrf2, Nurr1, and PPARγ, and how they are affected by exposure to pyrethroids. We conclude with possibilities to be addressed by future research of novel methods of protection against neurological disorders caused by pesticides that may also find their use in the management/treatment of Parkinson's disease.

KEY WORDS: cypermethrin; deltamethrin; Nrf2; Nurr1; Parkinson's disease; permethrin; pesticides; PPARγ

Pesticides are a major group of chemicals extensively used throughout the world to kill, repel, or control pests. They include fungicides, rodenticides, herbicides, and insecticides. Human exposure to these compounds is inevitable because of pesticide residues in agricultural products and the environment. Pesticides can disrupt the function of different organs in the human body and affect the endocrine, reproductive, renal, immune, cardiovascular, respiratory, and nervous systems.

A number of epidemiological and experimental studies have confirmed the association between exposure to pesticides and the development of neurodegenerative diseases (1–4), which are characterised by progressive degeneration of the structure and function of neurons (5). Several have also confirmed the association between pesticides (such as pyrethroids, organophosphates, and organochlorines) and Parkinson's disease (6–10), characterised by the disappearance of nigrostriatal dopaminergic neurons in the *substantia nigra pars compacta* (SNpc) and the presence of intraneuronal proteinaceous cytoplasmic inclusions, also known as Lewy bodies (LBs) (11).

Pesticides induce disorders through several mechanisms of action such as inflammation, oxidative stress, mitochondrial dysfunction and cell death (12). The aim of this review is to clarify those involved in neurotoxicity induced by pyrethroids (deltamethrin, cypermethrin, and permethrin) and propose the course of future investigations to improve our understanding of the problems at hand and protection against pyrethroid-induced neurotoxicity.

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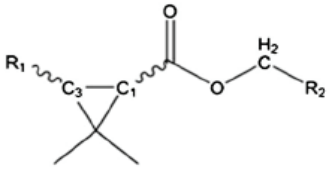
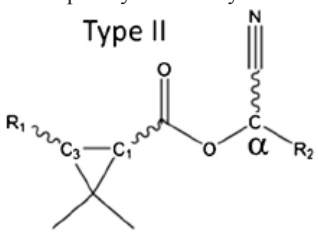
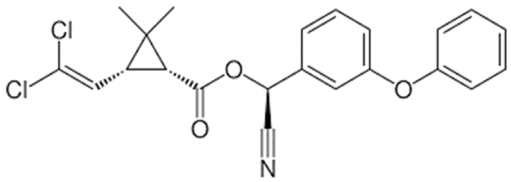
PYRETHROIDS

Pyrethroids are a class of synthetic insecticides based on pyrethrins isolated from the *Chrysanthemum* genus of plants (6). These pesticides consist of an acid moiety, a central ester bond, and an alcohol moiety. The acid moiety has two chiral carbons (trans and cis), which makes pyrethroids stereoisomeric (Figure 1). The toxic effects of the cis isomers are typically stronger than those of the trans isomers (13). Pyrethroids are therefore divided in two types (type I and II) according to their toxicity and structural characteristics (Table 1) (6, 14).

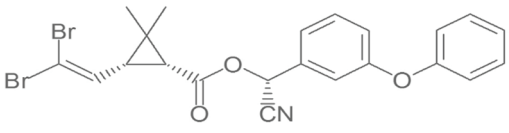
In vivo and *in vitro* studies (Tables 2 and 3) suggest that the main target of pyrethroid-induced neurotoxicity are voltage-gated sodium channels. Pyrethroids connect to the sodium channel α subunit and decelerate the stimulation of the channels. The channel remains active for a longer period of time, permitting more sodium ions to pass and depolarise neuronal membrane (6, 14, 47). The secondary targets of pyrethroid neurotoxicity are calcium and chloride channels (48). Type II pyrethroids, such as deltamethrin and cypermethrin, bind to GABA-gated chloride channels and

Table 1 Toxicity symptoms and structural characteristics of pyrethroids pesticides

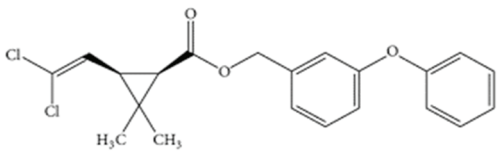
Pesticide type	Structure	Physiological effects and symptoms	Some of the pyrethroid pesticides	Ref.
Type I (tremor or T syndrome)	A cyano moiety at the α-position (α-cyano) Type I 	Behavioural arousal, hyperexcitation, ataxia, aggressive sparring and fine body tremor developing to whole-body tremor	Permethrin Allethrin Cimethrin Bifenthrin Bioallethrin	(6, 14)
Type II (choreoathetosis with salivation or CS)	With an alpha-cyano moiety Type II 	Hypersensitivity, coarse tremor progressing to choreoathetosis, profuse salivation and clonic seizures	Deltamethrin Cyfluthrin Cyhaluthrin Cypermethrin Tralomethrin Flucythrinate	(6, 14)



Cypermethrin



Deltamethrin



Permethrin

Figure 1 Structures of cypermethrin, deltamethrin, and permethrin

inhibit them (14, 49). The main concern about exposure to pyrethroids is the development of progressive neurodegenerative disorders (50). Due to its lipophilic nature, for example, deltamethrin can reach the brain in amounts that are probably toxic (15). Numerous investigations have indicated that it increases the risk of neurodegenerative diseases (51–54), as it inhibits nerve impulse by altering voltage-sensitive sodium channel kinetics and ligand-gated ion channels (GABA receptors, nicotinic acetylcholine receptors, and glutamate receptors) (14, 54). Its toxicity in the brain has been demonstrated in rats through the inhibition of acetylcholinesterase (AChE) activity (16, 17). Probably due to its lipophilic nature, deltamethrin inhibits AChE activity by reducing the acetylcholine binding space at the aromatic, hydrophobic surface of AChE (17, 55).

Cypermethrin is also lipophilic and involved in the pathogenesis of various neurological disorders as it accumulates in the brain (18, 56). A high concentration of cypermethrin in the brain leads to symptoms of neurobehavioral toxicity (57). Studies in rats have shown that cypermethrin leads to the loss of dopaminergic neurons in the *substantia nigra* and of the striatal dopamine content (19–21, 58, 59) through oxidative damage, inflammation, and apoptotic cell death (19). Its main target in humans is the voltage-gated sodium channel (VGSC), but chloride channels, voltage-gated calcium channels (VGCC), and potassium channels are also targeted (50).

Permethrin is a type I pyrethroid used to control woodworms indoors and outdoors (60). Like other pyrethroids, permethrin affects the sodium channels, neurotransmitters, and receptor-ionophore complexes (61).

There is increasing evidence of its association with neurological disorders (1). Recent studies in rats suggest that the neurotoxicity it causes is the most devastating in the early stages of development when the signalling pathways are formed (22, 23, 62, 63). Permethrin has been reported to increase α-synuclein, decrease striatal dopamine levels, induce oxidative stress, and inhibit mitochondrial complex I of the electron transport chain (24, 64-67). All of these changes in the striatum are the hallmarks of Parkinson's disease (66). In fact, the Parkinson's disease model induced by permethrin in the studies referenced above is suitable for investigating the initial markers of the disease which may help to find new ways to manage it (22).

Pyrethroids are metabolised by oxidation mediated by cytochrome P450 (CYP450) enzymes (37). In the brain, it is CYP2E1 that acts against environmental chemicals and plays a vital role in neuronal detoxification (68, 69). However, its overexpression in the brain tissue, as reported by Galal et al. after deltamethrin treatment (25), could increase the risk of neurotoxicity. Singh et al. (70) reported significantly increased levels of CYP2E1, CYP1A1, CYP2B1, and CYP2B2 in the hypothalamus, cerebellum and hippocampus of rat offsprings after prenatal treatment with high amounts of cypermethrin (2.5 or 5.0 mg/kg). In another study (71), the same group investigated the prenatal effects of low doses of cypermethrin on CYP2D1 and CYP3A1 expression in the brain of rat offspring. The mRNA and protein expression of CYP2D1 or 3A1 were increased, whereas the mRNA and protein expression of GABAergic, muscarinic, and dopaminergic receptors was decreased. Such reduction in dopaminergic receptors has been reported in Parkinson's disease (72). The authors concluded that changes in CYP2D1 and 3A1 may be closely associated with changes in these neurotransmitter receptors. Other authors also found the association between these CYPs and adjustments in the neurotransmission pathways (73), but further research is needed to establish the correlation between cytochrome isoenzymes and neurotransmitter receptors more precisely.

MECHANISMS OF PYRETHROID NEUROTOXICITY

Oxidative stress

Oxidative stress is the result of imbalance between free radical production and antioxidant defence (52) and is considered the key mechanism of pesticide toxicity (74). In exposed animals, free radicals such as superoxide anion, hydroxyl radicals, and hydrogen peroxide (H_2O_2) are produced by the metabolism of pyrethroids (37). Oxidative stress seems to particularly target the brain because of its high capacity to consume oxygen (51). Several studies reported it as the main mechanism of deltamethrin toxicity in rat brains (75, 76). Deltamethrin exposure also increases nitric oxide (NO•) and lipid peroxidation (LPO), as determined through its marker malondialdehyde (MDA) (51, 70, 77). Romero et al. (37) were the first to show that deltamethrin metabolites 20-OH- and 40-OH-deltamethirn were in fact more toxic than the parent compound to SH-SY5Y neuroblastoma cells.

Oxidative damage in rat brain and other tissues was also reported for cypermethrin (78, 79). Singh et al. (19) identified higher nitrite (an indicator of nitrosamine stress) and lipid peroxide (LPO, an indicator of oxidative stress) levels in the nigrostriatum. Nitrite and LPO were also significantly increased in the peripheral blood of rats exposed to cypermethrin dose that induces nigrostriatal dopaminergic neurodegeneration (26).

On the other arm of the oxidation balance, deltamethrin was reported to substantially decrease antioxidative activities of SOD, CAT, and GPx, and GSH in rat brain tissue (16, 17, 27). Similar effect on antioxidant enzymes was reported for cypermethrin (80 mg/kg, single dose) (79).

Oxidative stress caused by pyrethroids triggers important signalling pathways, including Nrf2 and NF-κB, and it can also induce mitochondrial dysfunction that leads to apoptosis (Figure 2).

Inflammation

Microglia (the resident macrophages in the brain) play a key role in preserving the normal function of the brain. M1 microglia (pro-inflammatory microglia) defend against pathogens by producing pro-inflammatory cytokines and proteins, including tumour necrosis factor alpha (TNFα), interleukin 12a (IL12a), CD16 (Fc receptor, FcyRIII), and inducible nitric oxide synthase (iNOS). M2 microglia (anti-inflammatory microglia), in turn, produce various neuroprotective components like insulin-like growth factor 1 (IGF1) and brain-derived neurotrophic factor (BDNF) (80). Excessive microglial activation, which leads to production of free radicals, cytokines, and chemokines (81), is associated with Parkinson's disease (82). There are plenty of reactive microglial cells in the *substantia nigra* and striatum of patients with Parkinson's disease (83). Microglial activation and subsequent overexpression of pro-inflammatory proteins triggered by cypermethrin show that inflammation is the key to degeneration of the nigrostriatal dopaminergic neurons (20, 21, 59), and NF-κB is the main transcription factor that regulates the genes involved in pro-inflammatory responses (84). In normal conditions, NF-κB remains bound to an inhibitory protein called IκB (inactive) in the cytoplasm (85). External stimulation, however, triggers IκB phosphorylation through the IκB kinase (IKK) complex. NF-κB translocates into the nucleus and stimulates downstream gene transcription (86), inducing the response of proinflammatory cytokines such as IL-1b and TNF-α (87).

There are some agents that modulate the NF-κB activity such as Nurr1 and calcium (Ca^{2+}), and they are both affected by pyrethroids. Ca^{2+} is vital for maintaining perfect neuronal

Table 2 *In vivo* pyrethroid studies

Species	Pesticide	Time of exposure	Dose	Effects	Result	Ref.
Rat	Deltamethrin	90 days	0.32 mg/kg	↓ GSH ↓ CAT and GPx ↑ Cyt-c, Cas-3 ↑ MDA	oxidative stress, apoptosis, mitochondrial dysfunction	(15)
Rat	Deltamethrin	14days	7.2 mg/kg	↑ MDA ↓ SOD, CAT, GPx activities ↓ AChE activity	oxidative stress	(16)
Rat	Deltamethrin	28 days	1.25 mg/100g	↓ AChE activity ↓ SOD and CAT activity	oxidative stress	(17)
Wistar rats	Cypermethrin	30 days	12 mg/kg	↓ AChE ↓ Monoamine oxidase (MAO) activity ↑Thiobarbituric acid-reactive substances (TBARS) ↓ GSH ↓ GST, GPX, CAT and SOD	necrosis apoptosis	(18)
Wistar rats	Cypermethrin	Twice a week (1.5 mg/kg) during postnatal days 5–19. Two months later, 12 weeks (15 mg/kg)		↓ Dopaminergic neurons ↑ Bax, caspase-3, cytochrome C ↑ COX-2, p53, ↑ JNK, ERK1/2, p38 MAPK ↑TNF-α	apoptosis oxidative stress inflammation	(19)
Male rats	Cypermethrin	Twice a week (1.5 mg/kg) during postnatal days 5–19. Two months later, 12 weeks (15 mg/kg)		↑ JNK, p38 MAPK ↑ p53, caspase-3 ↑ TNF-α, HO-1 ↓ Bcl-2	mitochondrial dysfunction, apoptosis	(20)
Wistar rats	Cypermethrin	5–19 days	1.5 mg/kg	↓ Number of TH-positive cells ↓ Dopamine content ↑ α-synuclein ↑ LPO, NO ↑ Cyt-c, caspase- 3 ↓ Bax	oxidative damage, mitochondrial dysfunction and apoptosis	(21)
Male and female Wistar rat	Permethrin	15 days PND6 to PND21	34.05 mg/kg	↓ DA ↓ Dopaminergic neurons	cognitive impairment, deterioration in locomotor performances	(22)
Male and female Wistar rats	Permethrin	15 days PND6 to PND21	34.05 mg/kg	↓ Dopamine and 5-HT ↑ Dopaminergic and serotonergic turnover (↑ HVA,a dopamine metabolite,↑ 5-HIAA, a 5-HT metabolite) ↑ NE ↓ NE turnover ↓ MHPG (a NE metabolite)	cognitive disorder	(23)

Species	Pesticide	Time of exposure	Dose	Effects	Result	Ref.
Male and female Wistar rats	Permethrin	15 days PND6 to PND21	34.05 mg/kg	↓ Nurr1 (in striatum) ↓ Glutamate (in hippocampus) ↓ Ca^{++} (in striatum and hippocampus) ↓ NO (in striatum and hippocampus) ↑ NO (plasma) ↓ SOD (plasma)	oxidative stress	(24)
Rat	Deltamethrin	30 days	0.6 mg/kg	↑ MDA ↑ NO ↑ TP53 mRNA ↑ COX2 ↑ CYP2E1	oxidative stress apoptosis	(25)
Wistar rats	Cypermethrin	Twice a week (1.5 mg/kg) during postnatal days 5–19. Two months later, 12 weeks (15 mg/kg)		↑ Nitrite (end product of nitric oxide) ↑ LPO ↓ GST activity (plasma) ↓ SOD activity (PMNs) ↓ Catalase activity (plasma)	oxidative stress	(26)
Rat	Deltamethrin	15 days	10 mg/kg	↑ MDA ↓ GSH ↓ SOD activity	oxidative stress	(27)
Male and female Wistar rats	Permethrin	15 days	34.05 mg/kg	↓ Nurr1 (striatum) ↑ Nurr1, Nrf-2 and NF-κB p65 (cerebellum) ↓ NO (cerebellum) ↑ Ca^{++} (striatum, cerebellum) ↓ Glutamate (cerebellum)	dopaminergic neuronal disorders	(28)
Rat	Deltamethrin	7 days	12.5 mg/kg	↑ Bax ↓ Bcl-2	apoptosis	(29)
Fish Common carps	Cypermethrin	3 days	(0.01,0.005) ppm	↑ Caspase 3, caspase 8 ↑ iNOS	inflammation apoptosis	(30)
Male mice	Cypermethrin	18 days	20 mg/kg	Inhibition of AChE activity ↑ H2O2 ↑ MDA	oxidative stress	(31)
Wistar rats	Cypermethrin	Twice a week (1.5 mg/kg) during postnatal days 5–19. Two months later, 12 weeks (15 mg/kg)		↑ Ulk 1, Beclin 1, Atg 12 ↑ p62 accumulation ↑ LC3 II ↓ LAMP 2	aberrant autophagy	(32)
Wistar rats	Cypermethrin	7 days	3.83 mg/kg	↑ LPO ↓ GSH ↓ SOD, CAT, GST, GR, and GPx ↓ AChE	oxidative stress	(33)
Zebra fish	Deltamethrin		2 mg/mL	↓*drd1mRNA* ↑*th* ↑HVA (metabolite of dopamine)	dopaminergic dysfunction	(34)
Mice	Cypermethrin+ Deltamethrin	E10.5 to E16.5	1.2 mg/kg	↑ Bax ↓ Bcl-xl	apoptosis	(35)
Male Wistar rats	Permethrin	60 days	150 mg/kg	↓ GSH	oxidative stress	(36)

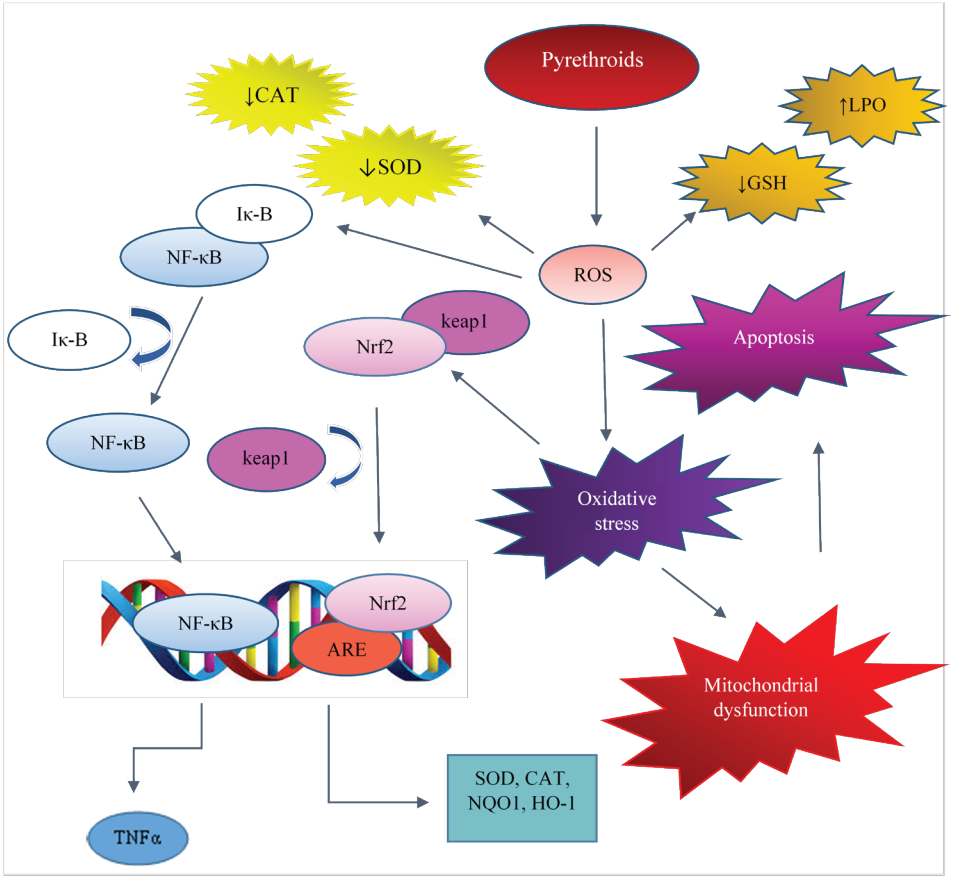


Figure 2 Production of ROS on one hand and reduction of enzymatic antioxidants (SOD, CAT, GPx) and non-enzymatic antioxidant (GSH) induce oxidative stress that leads to mitochondrial dysfunction and apoptosis

activity. Yet, high NF-κB activity can increase neuronal and glial Ca^{2+} concentration, as shown in the prefrontal cortex of 500-day-old rats exposed to permethrin in early life (28). Nurr1, in turn, exerts its anti-inflammatory role by repressing NF-κB activity in brain microglia (87).

The pro-inflammatory cytokine TNFα has been suggested to moderate the entire cytokine network. It is regulated by NF-κB, and its production can later enhance the activation of NF-κB (86). At higher levels TNFα can cause oxidative stress via ROS accumulation (88), and several studies have demonstrated that cypermethrin can increase the levels of TNFα (19, 20, 89). Cypermethrin has also been demonstrated to increase IL-1 levels in brain striatum (90). The use of NF-κB signalling pathway inhibitors can therefore decrease pyrethroid-induced neurotoxicity.

Mitochondrial dysfunction

The mitochondrion is an important organelle, as it regulates cell functions such as metabolism, membrane potential, and apoptosis (77, 91). ROS and oxidation damage mitochondrial DNA, disrupt its respiratory chain, and affect membrane permeability (92). Several studies have shown that mitochondrial dysfunction is involved in the aetiology of neurodegenerative disorders, including Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and Parkinson's disease (93, 94). Mitochondrial dysfunction is associated with α-synuclein aggregation in PARK2 iPSC-derived neurons (95). Pyrethroids seem to affect mitochondrial membrane potential and complex I action, as evidenced in the *substantia nigra* and striatum of cypermethrin-exposed rats (20, 21). Cypermethrin has also been shown to change mitochondrial proteome profile in the *substantia nigra* and striatum of rats (Table 4) (20). Similar was observed with mitochondrial Cyt-c and cytosolic Bax proteins, whose levels dropped substantially in cypermethrin-treated animals (21). These changes in the pattern of protein expression reflect abnormal mitochondrial function leading to the nigrostriatal dopaminergic neurodegeneration (96, 102, 103).

Apoptosis

Apoptosis or programmed cell death is triggered by toxins (104), radiation (105), hypoxia (106), oxidative stress (107), ischaemia/reperfusion (108), and DNA damage (109). The mitochondrial (intrinsic) pathway and death receptor (extrinsic) pathway are the two main signalling pathways inducing apoptosis (110). The mitochondrial pathway has been suggested as the main apoptosis pathway

Table 3 *In vitro* pyrethroid studies

Type of cell	Pesticide	Dose	Effect	Result	Ref.
SH-SY5Y cells	Deltamethrin and its main metabolites	10 μmol/L	↑ NO ↑ MDA	oxidative stress	(37)
PC12 cells	Deltamethrin	10 μmol/L	↑ Nrf2 ↑ HO-1 ↑ ROS	DLM increases ROS and subsequently increases Nrf2 expression and activity	(38)
SH-SY5Y cells	Deltamethrin	50–250 μmol/L	↑ cytochrome *c* ↑ caspase-9 ↑ Bax ↓ Bcl-2 ↑ PINK1(in mitochondria)	mitochondrial dysfunction apoptosis	(39)
PC12 Cells	Deltamethrin	10–100 μmol/L	↑ LDH ↓ DA(dopamine) ↑ Caspase-9 and -3 ↑ Beclin-1, p62, and LC3-II ↑ ROS ↑ ERK1/2, p38, and JNK activity	apoptosis autophagy	(40)
PC12 cells	Permethrin	1 μmol/L (72 h)	↑ Nurr1	pro-oxidant activity of the pesticide lead to *Nurr1* up-regulation, that significantly reduced in the presence of antioxidants	(41)
PC12 cells	Cypermethrin+ Deltamethrin	1 μmol/L DM and 100 μmol/L CP	↑ Bax ↓ Bcl-xl	apoptosis	(35)
SH-SY5Y cell line	Cypermethrin	0–200 μmol/L for 3 days	↑ LDH	necroptosis	(42)
SH-SY5Y cells	alpha-cypermethrin	1–100 μmol/L	↑ MDA ↑ NO ↑ LDH ↑ AKT1; APAF1; ATG3; ATG5; ATG7; ATG12; ATP6V1G2; BCL2; BCL2L1; BIRC2; BMF; CASP3; CASP7; CASP9; COMMD4; CTSB; CYLD; DENND4A; FAS; GADD45A; HSPBAP1; HTT; IGF1R; JPH3; MAP1LC3A; MAPK8; NFKB1; NOL3; PARP2; SNCA; SPATA2; SQSTM1; SYCP2; TXNL4B; ULK1; and XIAP genes ↓ GRB2, PARP1 and TP53	oxidative stress apoptosis autophagy necrosis	(43)
PC12 cells	Cypermethrin	1–300 μmol/L	↓ BCL2 ↑ miR-200a/b/c ↑ P53	apoptosis mitochondrial dysfunction	(44)
SH-SY5Y cells	Chlorpyrifos + Cypermethrin	(17.5+1.75, 25+2.5, 30+3.0 μmol/L)	↑ Caspase 3	apoptosis (TNF-α receptors contribute to the induction of SH-SY5Y cells apoptosis)	(45)
PC12 cells	Deltamethrin	1–100 μmol/L	↓ Dopamine ↓ TH	↓ dopamine biosynthesis	(46)

Table 4 Mitochondrial protein expression pattern after CYP exposure

Source of the mitochondrial protein	Protein name	Decrease	Increase	Effect	Ref.
Striatum	PDHE1-β	+		impairment in mitochondrial transport and energy metabolism	(20)
	NDP kinase A	+			
Substantia nigra	DLAT	+			
	α-tubulin		+		
Substantia nigra	ATP5D	+		impairment in electron transport chain and energy metabolism	(59)
Striatum	NDUFV2	+			
	IDH-NAD α	+			
Substantia nigra	PEBP1	+		impairment in neuronal repair and growth	(96)
Striatum	GNB-2		+	indicated in neurological disorders and PD	(96)
Substantia nigra	γ-enolase	+			
Striatum	Hsp-70	+		apoptosis	(97)
Substantia nigra	COX 5a	+		effect on mitochondrial complex 5	(98)
Striatum	COX VIa (AA 1–118)	+			
	COX VIa (85 AA)	+			
Substantia nigra	Cu-Zn SOD	+		oxidative damage and apoptosis	(99, 100)
Striatum	Prx2	+		redox cycling alternation	(101)
Substantia nigra	Prx3	+			

induced by pesticides such as paraquat (111), and various studies have shown that exposure to pyrethroids significantly affects the survival of neurons in rat brain through mitochondrial apoptosis (112, 113).

Pyrethroids can trigger apoptosis through ROS such as H_2O_2 or $OH^{\bullet}$ (38, 75, 114) and cytotoxins (77, 115). Deltamethrin has been evidenced to induce apoptosis in the neuronal cells of the cerebral cortex, hippocampus, and striatum (15, 29).

Apoptosis can also be triggered through mitochondrial damage and activation of caspase-3 and -9, as evidenced for deltamethrin in SH-SY5Y cells (39). Caspase-3 has a vital function in both extrinsic and intrinsic pathways of apoptosis (116, 117). In a study by Gasmi et al. (15), exposure to deltamethrin resulted in higher cytochrome c and caspase-3, followed by apoptosis, which confirmed mitochondrial damage (swelling and permeability).

Tumour protein p53 also plays a critical role in apoptosis (118). Stress signals such as DNA damage can enhance the otherwise low content of p53, which, in turn, increases the levels of the apoptotic gene (COX2) normally expressed in the brain (119, 120). This has been confirmed by Galal et al. (25), who reported that deltamethrin increased the mRNA expression of p53 and COX2. Cypermethrin was also reported to increase the expression of p53 (along with caspase-3) in rat striatum and *substantia nigra* (19, 20), and these findings were associated with apoptosis. One *in vitro* study in common carp brain cells (30) suggested that cypermethrin could induce apoptosis through the extrinsic pathway, judging by the elevated caspase 8 levels.

One of important pathways regulating apoptosis involves mitogen-activated protein kinases (MAPKs) (121), which are also involved in the development of neurodegenerative disorders (121, 122) and have been reported in pesticide-induced apoptosis in human neuroblastoma cells (SH-SY5Y) (123). In another study (20), cypermethrin increased the expression of p38 MAPK in the striatum and *substantia nigra*. Park et al. (40) reported MAPK cascade activation in deltamethrin-induced neuronal cell death through oxidative stress.

NEUROPROTECTIVE MECHANISMS AND PYRETHROID TOXICITY

Keap1/Nrf2/ARE pathway

An efficient repressor system to keep homeostasis (124) is the Keap1-Nrf2 pathway, which triggers the Antioxidant Response Element (ARE), which, in turn, is involved in the expression of antioxidant enzyme genes (124–126). Under oxidative stress, multiple cysteines on Keap1 react with reactive oxygen species (ROS) and lead to a conformational change that releases Nrf2 (127). Nrf2 separates from Keap1 and accumulates in the nucleus to stimulate the expression of several phase 2 drug metabolising enzymes and antioxidant genes (128).

In rat brain exposed to deltamethrin Nrf2 activates the HO-1 gene *in vitro* and *in vivo* (75, 129). Li et al. (38) confirmed nuclear Nrf2 accumulation and gene expression of HO-1 after exposure to deltamethrin in PC12 cells. Their study has demonstrated for the first time that Nrf2 is triggered by pesticides in PC12 cells and implicated in dopaminergic neuronal cell response to pesticide neurotoxicity. In fact, Nrf2 translocation into the cell nucleus is a response to deltamethrin-induced free radicals (38) and is an attempt to reduce oxidative stress. However, this Nrf2 translocation effect may be inadequate to protect against pyrethroid-induced neurotoxicity. This transcription factor also regulates the genes involved in anti-inflammatory responses. In a study by Carloni et al. (28), Nrf2 gene expression increased after exposure to permethrin in the cerebellum alongside with Nurr1, NF-κB, and Ca^{2+}. All these findings suggest that future research could focus on these beneficial properties of Nrf2 in the treatment of neurotoxicity.

Peroxisome proliferator-activated receptors

One of the neuroprotective signalling pathways against pyrethroid-induced toxicity and apoptosis involves peroxisome proliferator-activated receptors (PPARs) including PPARγ, PPARα, and PPARβ/δ. All three PPAR subgroups are believed to regulate gene expression by attaching to response elements (PPREs) in promoter genes. PPARγ regulates mitochondrial function and is extensively expressed in the basal ganglia, piriform cortex, and dentate gyrus of the brain (130). Growing evidence indicates that PPARγ agonists have a neuroprotective role in various animal neurodegeneration models (131–133). Furthermore, Juyeon et al. (39) have reported that rosiglitazone (PPAR-γ agonist) defends against deltamethrin-caused putative kinase 1 (PINK1) mediated apoptosis by suppressing cytosolic PINK1 translocation into mitochondria.

Autophagy

Autophagy has a vital role in eliminating damaged organelles to preserve cell homeostasis (134) and has been reported to protect against deltamethrin neurotoxicity through inhibition of apoptosis (40) (Figure 3). It also has an important role in protecting against neurotoxicity induced by an environmental stressor (135). If it is downregulated, misfolded α-synuclein proteins may aggregate in the neurons, which has been observed in neurodegenerative disorders such as Parkinson's disease (136). Other studies confirm that autophagy removes accumulated α-synuclein associated with Parkinson's disease (137–139).

One of the key regulators of autophagy is a kinase called mechanistic target of rapamycin (mTOR). It plays a role in the phosphorylation of ULK1, which activates autophagy by Beclin 1 phosphorylation (140). Figure 4 shows different proteins and molecules involved in autophagy.

Exposure to pesticides was reported to impair autophagic flux and subsequent increase in α-synuclein accumulation (141, 142). Mishra et al. (32) demonstrated that increased Beclin 1, Atg 12, and ULK1 levels and LC3-I conversion to LC3-II in cypermethrin-exposed rats, pointed to the formation of autophagosome, but LAMP2 reduction indicated that despite autophagosome formation, autophagy was disturbed because of poor lysosome quality and acidification. These findings suggest that components that regulate autophagy can be useful against cypermethrin-induced disruptions of autophagy.

Nurr1 and permethrin neurotoxicity

Nurr1 (also known as NR4A2) is an orphan nuclear receptor NR4A that has been demonstrated to regulate dopaminergic neuron development and survival (143). Nurr1 stimulates the transcription of tyrosine hydroxylase (TH) and dopamine active transporter (DAT), which are involved in dopamine biosynthesis and storage, respectively (143). Nurr1 reduction caused by accumulation of α-synuclein has been reported to lead to dopamine neuron dysfunction and downregulation of the *Nurr1* gene in the *substantia nigra* and striatum has been reported in patients with Parkinson's disease (144–148).

Nurr1 expression declines with age (149). Carloni et al. (24) reported lower *Nurr1* mRNA and protein in the striatum of adult (300-day-old) rats exposed to permethrin from postnatal day 6 to 21 in comparison with the control group. In another study, the same authors reported *Nurr1* downregulation and at the same time increased Nurr1 protein content in the striatum of 500-day-old rats treated with permethrin from postnatal day 6 to 15 (28), which points to a post-transcriptional compensation mechanism and reduction of Nurr1 ubiquitinylation. Bordoni et al. (150), in contrast, reported that neonatal treatment with permethrin resulted in enhanced *Nurr1* gene expression in adolescent rats, which they later confirmed with an upregulation of the *Nurr1* gene and its protein level in permethrin-treated PC12 cells (41). The authors suggested

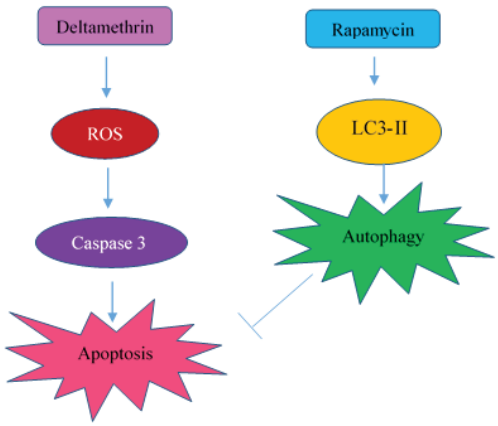


Figure 3 Apoptosis is inhibited after exposure to an autophagy inducer. Autophagy could be a therapeutic strategy against pyrethroid-induced neurotoxicity

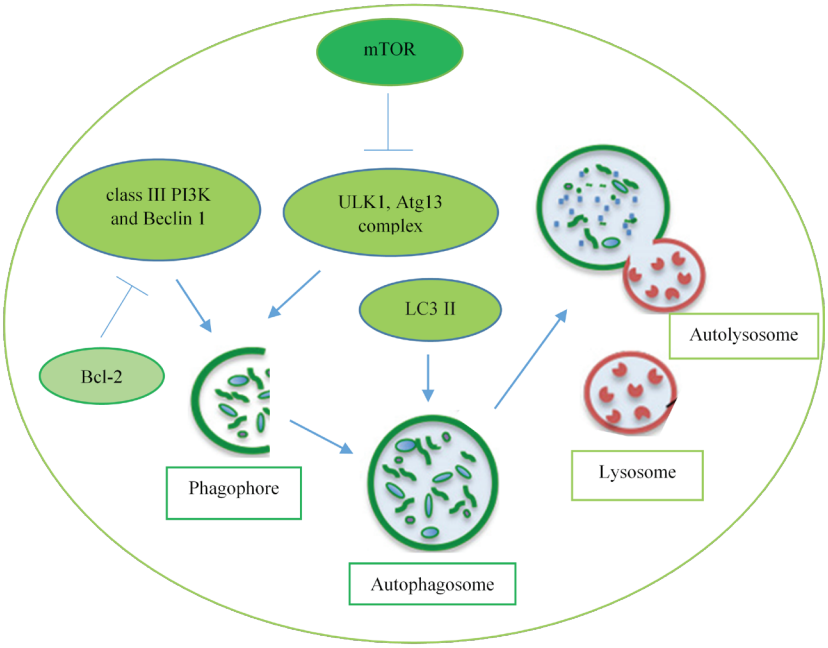


Figure 4 Summary of the autophagy pathway in stressful conditions. Inhibition of mTOR leads to ULK1 activation, which activates Beclin 1 phosphorylation and separation from Bcl-2. Beclin 1 is necessary for phagophore nucleation. Atg12 and LC3 conjugation systems are required for the elongation of the phagophore membrane. Under physiological conditions, LC3 is in the cytosol in the form of LC3-I. When autophagy starts, LC3-I binds to phosphatidylethanolamine (PE) and converts into LC3-II, which forms a steady association with autophagosome membrane. Phagophore elongates around a damaged cellular component and encloses it, forming an autophagosome, which fuses with a lysosome to form an autolysosome. In the lysosome, the cellular component is degraded by acid hydrolases

that permethrin may have enhanced *Nurr1* expression through its pro-oxidant activity. However, more studies are required to clarify the mechanisms related to exposure to pyrethroids and change in *Nurr1* gene expression.

CONCLUSION

Considering evident pyrethroid neurodegenerative effects common in Parkinson's disease, the question arises whether they constitute a risk factor for its development. However, little is still known and all implications of an association between pyrethroids and Parkinson's disease come from experimental studies in animal models, and only an accumulation of future epidemiological knowledge could shed some light on the matter. In the meanwhile, our review points toward new paths of research of molecular mechanisms that could help against pyrethroid-induced neurodegenerative disorders and perhaps find their application in managing/treating Parkinson's disease. In that respect, signalling pathways such as Nrf2 and Nurr1 have a potential, but the effects of their agonists against pyrethroid-induced neurotoxicity have not yet been investigated. Promising are also the agents that reduce inflammation and apoptosis or improve autophagy, and lysosomal and mitochondrial function.

Conflicts of interest

None to declare

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Izloženost piretroidima i njihova neurotoksičnost: mehanicistički pristup

Piretroidi su skupina sintetskih insekticida u širokoj primjeni: u kućanstvima i poljoprivredi, šumarstvu i komunalnoj higijeni. Problem vezan uz njihovu primjenu, koji je danas u središtu znanstvene pozornosti, njihova je neurotoksičnost i propadanje nigrostrijatalnih dopaminergičnih neurona kakvo je zamijećeno kod Parkinsonove bolesti. Glavni su mehanizmi toga neurotoksičnoga djelovanja oksidacijski stres, upalni procesi, gubitak neurona i mitohondrijska disfunkcija, a ono najviše pogađa ionske kanale. No i drugi su receptori, enzimi i signalni putovi pogođeni odnosno sudjeluju u poremećajima izazvanima piretroidima. Cilj je ovoga preglednog rada rasvijetliti mehanizme neurotoksičnoga djelovanja piretroida deltametrina, permetrina i cipermetrina. Također se razmatra kako izloženost piretroidima djeluje na uobičajene ciljeve i putove liječenja Parkinsonove bolesti, uključujući Nrf2, Nurr1 i PPARγ, te na koja pitanja trebaju odgovoriti buduća istraživanja i nove metode zaštite od neuroloških poremećaja izazvanih ovim pesticidima.

KLJUČNE RIJEČI: cipermetrin; deltametrin; Nrf2; Nurr1; Parkinsonova bolest; permetrin; pesticidi; PPARγ