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World J Clin Cases 2023 August 26; 11(24): 5628-5839



MINIREVIEWS

- 5628 Effect of pesticides on phosphorylation of tau protein, and its influence on Alzheimer's disease
Torres-Sánchez ED, Ortiz GG, Reyes-Urbe E, Torres-Jasso JH, Salazar-Flores J

ORIGINAL ARTICLE

Case Control Study

- 5643 Reduction rate of monoclonal protein as a useful prognostic factor in standard-risk group of newly diagnosed multiple myeloma
Liu M, Zhang JY

Retrospective Cohort Study

- 5653 Effectiveness of treating menorrhagia using microwave endometrial ablation at a frequency of 2.45 GHz
Kakinuma T, Kaneko A, Kakinuma K, Matsuda Y, Yanagida K, Takeshima N, Ohwada M
- 5660 Benefits of laparoscopy-assisted ileostomy in colorectal cancer patients with bowel obstruction
Wang YJ, Lin KH, Kang JC, Hu JM, Chen CY, Pu TW

Retrospective Study

- 5666 Hypopharyngeal cancer trends in a high-incidence region: A retrospective tertiary single center study
Cordunianu AGV, Ganea G, Cordunianu MA, Cochior D, Moldovan CA, Adam R
- 5678 Relevant detection indicator of prethrombotic state in patients with primary hypertension
Luo J, Yang T, Ding L, Xiong JH, Ying T, Xu F
- 5692 Clinical study of extrahepatic biliary adenoma
Li W, Tao J, Song XG, Hou MR, Qu K, Gu JT, Yan XP, Yao BW, Qin YF, Dong FF, Sha HC

SYSTEMATIC REVIEWS

- 5700 Sodium-glucose cotransporter-2 inhibitor-associated euglycemic diabetic ketoacidosis in COVID-19-infected patients: A systematic review of case reports
Khedr A, Hennawi HA, Khan MK, Eissa A, Mir M, Rauf I, Nitesh J, Surani S, Khan SA

META-ANALYSIS

- 5710 Efficacy and safety of Huangqi Jianzhong decoction in the treatment of chronic atrophic gastritis: A meta-analysis
Yan XP, Si W, Ding MS, Tian YF, Guo Z

CASE REPORT

- 5721** Malignant melanoma of the prostate: Primary or metastasis? A case report
Zhao H, Liu C, Li B, Guo JM
- 5729** Intravenous leiomyoma of the uterus extending to the pulmonary artery: A case report
Huang YQ, Wang Q, Xiang DD, Gan Q
- 5736** Percutaneous endoscopic necrosectomy for walled-off necrosis in the retroperitoneal space of the elderly: A case report
Sato K, Shibukawa G, Ueda K, Nakajima Y, Togashi K, Ohira H
- 5742** Acute exacerbation of idiopathic pulmonary fibrosis treated using the Feibi recipe: Two case reports
Liu ZH, Li GD, Hao QX, Cao F, Cheng Y, Kou MJ, Jiao Y
- 5749** Neonatal erythema multiforme associated with a rotavirus infection: A case report
Kim JJ, Lee JK
- 5755** Hemorrhagic Bartholin's cyst in a woman using anti-platelet medication: A case report and review of the literature
Li YR, Ding DC
- 5762** Subintimal recanalization for non-acute occlusion of intracranial vertebral artery in an emergency endovascular procedure: A case report
Fu JF, Zhang XL, Lee SY, Zhang FM, You JS
- 5772** Synchronous rectal adenocarcinoma and intestinal mantle cell lymphoma: A case report
Vu KV, Trong NV, Khuyen NT, Huyen Nga D, Anh H, Tien Trung N, Trung Thong P, Minh Duc N
- 5780** Focal lymphoblastic transformation of chronic myelogenous leukemia develops into erythroid leukemia: A case report
Wang W, Chen YL, Gou PP, Wu PL, Shan KS, Zhang DL
- 5789** Intraoperative sudden arrhythmias in cervical spine surgery adjacent to the stellate ganglion: A case report
Seo JH, Cho SY, Park JH, Seo JY, Lee HY, Kim DJ
- 5797** Papillary thyroid carcinoma with nodular fasciitis-like stroma - an unusual variant with distinctive histopathology: A case report
Hu J, Wang F, Xue W, Jiang Y
- 5804** Malignant form of hidroacanthoma simplex: A case report
Yang YF, Wang R, Xu H, Long WG, Zhao XH, Li YM
- 5811** Penile and scrotal strangulation by stainless steel rings in an human immunodeficiency virus positive man: A case report
Usuda D, Kaminishi N, Kato M, Sugawara Y, Shimizu R, Inami T, Tsuge S, Sakurai R, Kawai K, Matsubara S, Tanaka R, Suzuki M, Shimozawa S, Hotchi Y, Osugi I, Katou R, Ito S, Mishima K, Kondo A, Mizuno K, Takami H, Komatsu T, Oba J, Nomura T, Sugita M

- 5817** Persistent postoperative hypotension caused by subclinical empty sella syndrome after a simple surgery: A case report
Zhao KM, Hu JS, Zhu SM, Wen TT, Fang XM
- 5823** Rare *ROS1-CENPW* gene in pancreatic acinar cell carcinoma and the effect of crizotinib plus AG chemotherapy: A case report
Wang T, Shen YY
- 5830** Fecal transplantation in patient with metastatic melanoma refractory to immunotherapy: A case report
del Giglio A, Atui FC
- 5835** Left hepatic artery pseudoaneurysm complicating endoscopic retrograde cholangiopancreatography: A case report
Li QM, Ye B, Yang SW, Zhao H

ABOUT COVER

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Effect of pesticides on phosphorylation of tau protein, and its influence on Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a progressive and neurodegenerative illness which results in alterations in cognitive development. It is characterized by loss/dysfunction of cholinergic neurons, and formation of amyloid plaques, and formation of neurofibrillary tangles, among other changes, due to hyperphosphorylation of tau-protein. Exposure to pesticides in humans occurs frequently due to contact with contaminated food, water, or particles. Organochlorines, organophosphates, carbamates, pyrethroids and neonicotinoids are associated with the most diagnosed incidents of severe cognitive impairment. The aim of this study was to determine the effects of these pesticides on the phosphorylation of tau protein, and its cognitive implications in the development of AD. It was found that exposure to pesticides increased the phosphorylation of tau protein at sites Ser198, Ser199, Ser202, Thr205, Ser396 and Ser404. Contact with these chemicals altered the enzymatic activities of cyclin-dependent kinase 5 and glycogen synthase kinase 3 beta, and protein phosphatase-2A. Moreover, it altered the expression of the microtubule associated protein tau gene, and changed levels of intracellular calcium. These changes affected tau protein phosphorylation and neuroinflammation, and also increased oxidative stress. In addition, the exposed subjects had poor level of performance in tests that involved evaluation of novelty, as test on verbal, non-verbal, spatial memory, attention, and problem-solving skills.

Key Words: Organochlorines; Organophosphates; Carbamates; Pyrethroids; Neonicotinoids; Tau protein

Core Tip: Exposure to pesticides occurs frequently through contact with contaminated particles, food, or water. In 2022, the Alzheimer's Association emphasized that contact with these pollutants is a risk factor for Alzheimer diseases. This study showed that contact with organochlorines, organophosphates, carbamates, pyrethroids and neonicotinoids modified mechanisms related to tau hyperphosphorylation and neuroinflammation. In cognitive findings, these chemicals altered memory, attention, and problem-solving processes. Few published studies have evaluated the effect of these pesticides on tau protein. Therefore, this review is novel in the sense that it presents an analysis for each pesticide class.

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INTRODUCTION

Alzheimer's disease (AD) represents 60%-70% of the cases of major cognitive disorders (MCD) worldwide. In 2022, data from the World Health Organization[1] showed that approximately 55 million people were diagnosed with MCD. Additional data from Alzheimer's Disease International indicate that by 2030, this figure may increase to 78 million, with most cases expected to come from developing countries[2]. Amongst the risk factors associated with the development and progression of AD, exposure to pollutants has been linked to poor cognitive impairment[3]. These pollutants comprise organochlorine (OCs) pesticides, organophosphates (OPs), carbamates (Cs), pyrethroids (Ps) and neonicotinoid insecticides (Ns). Majority of them have neurotoxic potential. Environmental pollution by pesticides occurs through airborne dust particles, resulting in frequent contamination of air, water and food. Approximately, 30% of these chemicals are dispersed in powder form, while the remaining 70% are volatilized into the environment from surfaces where they are applied[4-7]. Another indirect form of contact with these chemicals is through consumption of contaminated water and food. Previous studies from India, Brazil, Lithuania, Egypt, Turkey, Mexico, and Venezuela revealed presence of contamination in vegetables, fruits, cereals, and water *via* exposure to OCs, OPs, Cs, Ps and Ns[5,8-10].

Pesticides are organic and hydrophobic molecules which are easily absorbed through different routes of exposure in humans. Pesticides are distributed mainly in lipid tissues of the body where they bioaccumulate as residues[5,11]. It is important to note that the brain and central nervous system (CNS) are rich in lipids, mainly sphingolipids, cholesterol, glycerophospholipids and omega-3 and omega-6 polyunsaturated fatty acids[12]. Thus, the brain and CNS are anatomical sites vulnerable to pesticides due to physicochemical affinity[5,11]. Previous studies indicate that in CNS, exposure to pesticides alters neurogenesis and leads to cognitive impairment[13,14]. However, there is still doubt about the involvement pesticides in the development of AD, and the underlying pathophysiological mechanisms. Most of the published studies on patients with AD or in experimental models were focused mainly on evaluation of the effects of exposure to two classes of pesticides: OC and OP. There are limited reports on effect of exposure to Cs, Ps and Ns, and the impact of the pesticides on tau protein phosphorylation. Tau protein, which is expressed in the distal extremity of the axon, controls the stability of microtubules. Hyperphosphorylation of tau protein stimulates the dissociation of microtubules, interrupts axonal extension, and enhances the aggregation of insoluble tau, leading to alterations in the synapse, and hence tauopathy[15,16]. Therefore, the present study was aimed at investigating the effects of OC, OP, C, P and N pesticides on the phosphorylation of tau protein, and the associated cognitive implications in the development of AD.

PESTICIDES AND CNS EFFECTS

In a general way, the major reported effects of pesticide exposure on CNS are changes in enzymatic activity of acetylcholinesterase (AChE), blockage of receptors, blockage of transport channels, changes in steroidal hormonal responses, mitochondrial damage, and increased oxidative stress, all of which affect motor, sensory, autonomous, and cognitive functions[14,17,18]. Specifically, OC pesticides block calcium-dependent sodium-potassium pump and chloride channels, a phenomenon that generates antagonistic effect on the neurotransmitter gamma aminobutyric acid (GABA), leading to increases in CNS excitotoxicity[4,17,19]. On the other hand, OP and C pesticides inhibit AChE: OPs bind irreversibly to the active site of AChE, while Cs binds reversibly to AChE[4,17,18]. The inhibition of AChE increases the concentration of acetylcholine, thereby overstimulating postsynaptic muscarinic receptors[4,19,20]. Therefore, exposures to OP and C pesticides have been linked to the development of MCD through changes in acetylcholine levels[4]. The class P pesticides act *via* 3 different mechanisms. Firstly, they bind to voltage-dependent sodium channels, thereby modifying their conformations. This affects the transition from ion to non-conductive state which results in a higher sodium input. Secondly, they block the binding of calcium to calmodulin, resulting in increases in calcium ion concentration which alter the neurotransmission and depolarization of the N-methyl-D-aspartate receptor. Thirdly, they bind to chloride-dependent GABA receptors. These 3 mechanisms alter muscarinic, adrenergic, and serotonergic neurotransmissions,

resulting in symptoms such as tremor, prostration, sensitivity to stimuli, choreoathetosis, salivation and clonic seizures[4, 17,21]. The N pesticides are nicotinic receptor agonists in CNS postsynaptic neurons. The nicotinic receptors are part of important ion channels in the neurotransmission functions of acetylcholine, GABA, glycine, and glutamate. Therefore, exposure to N pesticides triggers nicotinic syndrome which involves the respiratory and cardiovascular functions, as well as CNS[4,17,22].

Other disturbances induced by pesticide exposure are linked to estrogen steroid receptors and steroid nuclear receptors. Interactions of pesticides with these receptors alter various metabolic and genetic pathways, which may lead to multiple pathologies, including AD[18,23]. It has been reported that several pesticides act as endococcal disruptors due to their ability to inhibit cytochrome P450 enzyme complex in the brain, with adverse impact on the synthesis of steroid hormones, vitamins, retinoic acid, and thyroid hormones[18]. It has been reported that exposure to hydroxychlor, an OC pesticide, resulted in antagonism of estrogen receptors alpha and beta, a situation which may lead to neurological alterations[24]. Besides, due to their hydrophobic characteristics, the OC and OP pesticides are easily incorporated into the mitochondria along with mitochondrial respiratory chain translocating proteins, leading to enhanced oxidative damage, increased mitochondrial permeability, induction of apoptosis, and decreased synthesis of ATP[25].

Additionally, pesticide-induced overactivation of cholinergic/glutamatergic responses and increased concentration of intracellular calcium ion, are associated with increased free radicals, mainly reactive nitrogen species and reactive oxygen species, thereby tilting the oxidant-antioxidant balance towards pro-oxidants[25,26]. A break in the mitochondrial oxidant-antioxidant homeostasis results in loss of neuronal synapses, as well as neuropathological, neurochemical, and neurobehavioral alterations[4].

PESTICIDES AND THEIR IMPACTS ON TAU PROTEIN

Tau protein and tauopathies

AD is characterized by loss of cholinergic neurons or dysfunctional cholinergic neurons, formation of amyloid plaques, and formation of neurofibrillary tangles, due to hyperphosphorylation of tau-protein[15,27]. Based on the objective of this work, the characteristics of tau protein and its response to exposure to pesticides are highlighted in this review.

Physiologically, the tau protein is involved in myelination processes[16,28], regulation of glucose metabolism[29], rearrangement of microtubules[16], axonal transport[16], iron homeostasis[16], as well as neurogenesis and processes related to learning and memory[16,28]. However, exposure to pesticides may affect the phosphorylation of tau protein and the formation of neurofibrils, resulting in morphological changes in CNS[30,31].

Tau protein is expressed in six different isoforms: 2N4R, 1N4R, 0N4R, 2N3R, 1N3R and 0N3R, depending on their amino and carboxyl groups. These isoforms come from the alternative cutting and splicing of the microtubule associated protein tau (*MAPT*) gene located on position q21 of chromosome 17[16,28]. Tau is a 441-amino acid hydrophilic protein sub-classified into 4 domains. The sites susceptible to phosphorylation correspond to the amino acids Ser198, Ser199 and Ser202[32]. The amino acids Thr181, Thr205 and Thr217 are associated with the early stages in the development of AD[16, 28], while amino acid residues Ser262, Ser396 and Ser404 are associated with formation of aggregates[31].

Tauopathies are pathologies that arise as a result of alterations in the phosphorylation of tau. Often, these alterations are the result of imbalance involving two kinases: Cyclin-dependent kinase 5 (Cdk5) and glycogen synthase kinase 3 beta (GSK-3 β), and protein phosphatase-2A (PP2A). The enzymes Cdk5 and GSK-3 β are responsible for phosphorylating tau protein, whereas PP2A dephosphorylates the protein. A close relationship has been reported between GSK-3 β and PP2A, both of which regulate each other. For example, when GSK-3 β is activated, PP2A is inactivated by auto-phosphorylation at its amino acid residue Tyr-307[28,32-34]. Moreover, the regulation of GSK-3 β also depends on routes modulated by calcium/calmodulin, and on the ratio guanosine-5'-triphosphate/guanosine diphosphate. Another important alteration in tauopathy is the phosphorylation of proteins associated with microtubules-2 (MAP-2) which are regulated by cyclic adenosine monophosphate. The MAP-2 is important in stabilizing microtubule assembly, and it is intimately bound to tau protein. Thus, it has been reported that multiple axopathies are associated with abnormalities in these pathways[35, 36].

In AD, increased hyperphosphorylation of tau forms aggregates in neuronal cytoplasm, resulting in generation of the so-called neurofibrillary tangles and neurotrophic neurites, which are responsible for neurodegeneration[28,31,37,38]. This phenomenon induces morphological changes in dendrites and causes axonal shortening which alters neuronal plasticity and response to neurotransmitters, leading to problems associated with spatial memory, motor skills and learning, all of which are characteristics of AD[33,34,39]. In addition, the release of tau aggregates in the cytoplasm increases immunoreactivity and oxidative stress which influence neuroinflammation[34,40]. Increased oxidative stress over-activates GSK-3 β , thereby making tau protein more vulnerable to formation of aggregates and new neurofibrils[41]. Results from multiple studies indicate that exposure to pesticides modifies the mechanisms involved in tau phosphorylation[32-34,42,43] (Figure 1).

Effect of OCs on the tau protein

Table 1 shows 7 studies in which the effect of OCs on tau protein phosphorylation was determined[42,44-49]. Two clinical studies reported that exposure to these pesticides may be associated with polymorphisms in *MAPT* and microtubule associated protein 1B gene which are related to the formation of tau aggregates[44,45]. Studies have demonstrated that dichlorodiphenyltrichloroethane exposure to an OC altered mitochondrial function, resulting in the formation of tau aggregates, with up-regulations in the expressions of proteins such as synaptosome-associated protein 25 kDa, cytochrome C, enolase A, hemoglobin alpha chain and histone cluster 1, which are characteristic of AD[42,46,47]. Finally,

Table 1 Effect of organochlorine pesticides on tau protein

Type of study	Sample	Type of pesticide	Exposure data	Tau phosphorylation	GSK-3 β	PP2A	Other mechanisms	Ref.
Clinical/epidemiological studies. Cohort	13 postmortem brains of humans without exposure, and 4 postmortem brains of humans with exposure	OCs	Concentration: NA. Exposure time: From 0 to 10 yr	Increased	NA	NA	Exposure altered mitochondrial genes encoding <i>MAPT</i> and <i>MAP1B</i> . These are associated with <i>MAPT</i> phosphorylation and neurite formation that contributed to the development of tauopathies	[44]
Clinical/epidemiological studies. Cross-sectional	90 subjects with PD, and 90 healthy subjects	δ -HCH	Concentration: NA. Exposure time: NA	NA	NA	NA	Exposure was associated with <i>MAPT</i> rs16940758 polymorphism which was related to tau aggregation	[45]
Experimental studies	Strains of <i>Caenorhabditis elegans</i> (N2 BR5270)	DDT	Concentration: 3 μ M. Exposure time of 2 h	Increased	NA	NA	DDT exacerbated tau protein toxicity, reduced mitochondrial respiration, and induced apoptosis	[42]
Experimental studies	Strains of <i>Caenorhabditis elegans</i> (N2 BR5271)	DDT	Concentration: 3 μ M. Exposure time of 2 h	Increased	NA	NA	Exposure to DDT increased tau protein aggregation and modified mitochondrial respiration	[46]
Experimental studies	Female largemouth bass	Dieldrin	Concentration: 3.0 mg/kg. Exposure time of 57 d	NA	NA	Decreased	Increased expression of proteins in hypothalamus such as Snap25, Cytc, Eno1, Hba1, and H2bb. These proteins were elevated in the pathophysiology of mice with AD and were associated with tau protein. Additionally, downregulation of <i>MAPT</i> was observed, which affected phosphatase activity	[47]
Experimental studies	Wistar rats	Chlordane	Range of concentration: 1 to 100 nM. Chronic exposure	Not modified	NA	NA	No significant changes in tau protein levels from exposure to chlordane	[49]
Review studies	Multiple studies	TCDD	Range of concentration: 5-23 ppt. Single dose	Increased	Increased	NA	Increased intracellular calcium levels and tau phosphorylation in neurons through overexpression of GSK-3 β and hence its enzymatic activity	[48]

OCs: Organochlorine; NA: Not available; MAPT: Microtubule associated protein tau; δ -HCH: δ -hexachlorocyclohexane; DDT: Dichlorodiphenyltrichloroethane; AD: Alzheimer's disease; TCDD: 2,3,7,8 tetrachlorodibenzo-p-dioxin; GSK-3 β : Glycogen synthase kinase 3 beta; PD: Parkinson disease; ppt: Parts per thousand; PP2A: Protein phosphatase-2A.

Mir *et al* [48] has shown that exposure to 2,3,7,8 tetrachlorodibenzo-p-dioxin induced overexpression of GSK-3 β , and hence tau phosphorylation. In all, 4 of the 7 studies described in Table 1 reported increases in tau phosphorylation [42,44,46,48]. Therefore, OCs have been associated with development of tauopathy which leads to axonal instability, mitochondrial dysfunction and neuroinflammation [44].

Effect of OPs on the tau protein

Exposure to OPs (chlorpyrifos, paraquat and malathion) increases the level of hyperphosphorylated tau protein, overstimulates glial cells, and increases the levels tumor necrosis factor- α , interleukin (IL)-6, IL- β , chemokines, NADPH oxidase 2, NADPH oxidase and COX-2, thereby inducing neuroinflammation. Intensified inflammation accelerates pathologies associated with neurodegenerative processes [33,40,50]. Similarly, when OP pesticides are transported through the blood-brain barrier, a process regulated by Na⁺ dependent transporters, microglia are activated, resulting in redox imbalance which affects the mitochondrial respiratory chain at mitochondrial complex I, leading to deterioration of CNS function [51,52]. Table 2 provides a breakdown of 18 studies on the effect of OPs on tau protein [31,33,36,37,39,41,49,50,51,53-61]. The only report on cases and controls with OP exposure for more than 2 years showed higher levels of tau phosphorylation in exposed subjects [53]. On the other hand, eight out of eleven studies indicate that exposure to these

Table 2 Effect of organophosphates pesticides on tau protein

Type of study	Sample	Type of pesticide	Exposure data	Tau phosphorylation	GSK-3 β	PP2A	Other mechanisms	Ref.
Clinical/epidemiological studies. Cases and controls, unpaired	33 humans exposed to OPs and 33 humans without exposure	OPs	Concentration: NA. Exposure time 2 yr	Increased	NA	NA	Subjects exposed to OPs for more than 10 yr showed 97% higher serum concentration of phosphorylated tau, when compared to the control group	[53]
Experimental studies	C57BL/6 and 129/Sv mice	Paraquat	Concentration: 10 mg/kg. Exposure time for 6 wk	Increased	Increased	NA	Exposed mice showed a 67% increase in hyperphosphorylation of tau in Ser262, Ser396 and Ser404 in striata region, suggesting that paraquat may inhibit the proteasome 20S as tau overexpression occurs. Thus, it was inferred that the proteosomal activity was reduced by exposure to paraquat	[31]
Experimental studies	Wistar rats	Malathion	Concentration: 100 mg/kg. Exposure time of 14 d	Increased	Increased	Decreased	The level of hyperphosphorylated tau protein in rats with exposure was increased in Thr205 and Ser404. This result may be related to phosphatase inactivation and increased GSK-3 β activity. In addition, a decrease in the expression of mRNA of PP2A was reported due to the exposure to malathion	[33]
Experimental studies	MAP-rich tubulin from Sus Scrofa from porcine brain	Chlorpyrifos-oxon, paraoxon and diazoxon	Concentration: 100 μ M. Exposure time of 48 h	Increased	NA	NA	Cross-link was formed between MAP-tubulin (alpha), at residues Lys163, Lys336 and Asp98 of MAP with residues Glu158 and Lys115 of tubulin beta. Lys336 and 163 cross-links covalently joined with tau protein, forming Lys-adduct, which resulted in unstable microtubules	[36]
Experimental studies	FVB and C57BL/6 mice	DFP	Concentration: 5 mg/kg. Exposure time of 15 d	Increased	NA	NA	Exposure increased Cdk5 activity by converting p35 to p25. Exposure to DFP increased 15.5 \pm 2 times the phosphorylation of Cdk5 in Thr205 and therefore of tau protein, thereby inducing neurological effects in the striatum and hippocampus	[37]
Experimental studies	Wistar rats	Chlorpyrifos-oxon	Range of concentration: 1 to 100 nM. Chronic exposure	Not modified	NA	NA	No significant changes in tau protein levels from chlorpyrifos exposure	[49]
Experimental studies	Transgenic AD model rats	Chlorpyrifos	Concentration: 3 and 10 mg/kg. Exposure time of 21 d	Not modified	NA	NA	No changes in hyperphosphorylation of rat tau protein with exposure to control rats	[50]
Experimental studies	Wistar rats	Paraquat	Concentration: 0.1 mg/kg. Exposure time of 4 mo	Increased	NA	NA	In exposed rats, neurofibrillary tangle was formed in the compact pars of the substantia nigra region and in extracellular neuritic plaques as a result of a neuroinflammatory cascade by the activation of microglia and astrocytes, which increased tau phosphorylation	[51]
Experimental studies	NMRI mouse	Chlorpyrifos	Concentration: 0.1, 1.0, 5.0	Not modified	NA	NA	No significant differences were observed in tau levels	[54]

			mg/kg. Single dose				due to exposure to this pesticide	
Experimental studies	Cell culture in septal SN56 basal forebrain cholinergic neurons	Chlorpyrifos	Concentration: 30 µM. 24 h and 14 d exposure time	Increased	Increased	NA	Exposure to OPs upregulated the expression of GSK-3β and its activity, thereby increasing the phosphorylation of tau	[55]
Experimental studies	Cell culture hiPSC and Wistar rats	DFP	Cell culture concentration: 200 nM. Exposure time for 2 d. Murine concentration: 1.5 mg/kg. Exposure time for 7 d	Increased	NA	NA	Exposure was associated with increased tau phosphorylation and decreased microtubule acetylation which decreased its stability. In the CA3 region of the hippocampus, an increase in tau phosphorylation was observed, indicating that it is a vulnerable site for the action of OPs	[56]
Experimental studies	Wistar rats	Dichlorvos	Concentration: 200 mg/kg. Single dose	Increased	NA	NA	Increased phosphorylation of MAP-2 and tubulin. Exposure increased phosphorylation and stimulated increased activity of calcium-dependent kinases/calmodulin and cAMP. Microtubules were destabilized, resulting in changes in morphology and increased neurotoxicity in exposed rats	[57]
Review studies	Multiple studies	Malathion	Range of concentration: 97 to 775 µM in model MCF-7. Concentration: 100 mg/kg in Wistar rats. Single dose	Increased	Increased	Decreased	MAP-2 hyperphosphorylation was observed, especially of KGS amino acids. This may be related to ubiquitination and protein degradation with these amino acids. Tau hyperphosphorylation is associated with GSK-3β kinase activation and phosphatase inhibition	[39]
Review studies	Multiple studies	Paraquat	NA	Increased	NA	NA	Paraquat raised levels of oxidative stress, thereby inducing phosphorylation of tau, based on several studies conducted in cell cultures	[41]
Review studies	Multiple studies	OPs	NA	Increased	NA	NA	Exposure to OPs increased Cdk5 hyperactivity and tau hyperphosphorylation. This disrupted the structure and function of microtubules in patients with AD, thereby affecting axonal transport. Even low levels of exposure caused changes in microtubules	[58]
Review studies	Multiple studies	OPs	NA	Increased	Increased	NA	Increased the level of reactivity autoantibodies against microtubule-associated proteins and tau-regulatory proteins (MAPT and MAP-2)	[59]
Review studies	Multiple studies	OPs ester	Different conditions	Increased	NA	NA	The activities of kinase enzymes were altered phosphorylation of Ser or Thr. This enhanced the aggregation of proteins and the formation of neurofibrils, thereby inducing neurodegeneration. The target enzymes are calcium/calmodulin dependent kinases that increase phosphorylation of MAP-2 and tau protein	[60]

Review studies	Multiple studies	Methamidophos, trichlorfon, dichlorvos, chlorpyrifos	Different conditions	Increased	NA	NA	Increased activity of calcium-dependent kinases/calmodulin, forming aberrations in the phosphorylation of cytoskeleton proteins, a common feature in neurodegenerative diseases	[61]
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OPs: Organophosphates; NA: Not available; DFP: Diisopropyl fluorophosphate; Thr: Threonine; K: Lysine; G: Glycine; S: Serine; Ser: Serine; mRNA: Messenger ribonucleic acid; hiPSC: Human-induced pluripotent stem cells; Lys: Lysine; Asp: Aspartate; Glu: Glutamate; MAPT: Microtubule associated protein tau; AD: Alzheimer's disease; TCDD: 2,3,7,8 tetrachlorodibenzo-p-dioxin; GSK-3 β : Glycogen synthase kinase 3 beta; MAP-2: Microtubules-2; Cdk5: Cyclin-dependent kinase 5; cAMP: Cyclic adenosine monophosphate; PP2A: Protein phosphatase-2A.

pesticides increased tau phosphorylation through different mechanisms involving GSK-3 β overexpression, increased Cdk5 activity, and decreased expression of PP2A, among other factors (Table 2). Six review studies described in Table 2 reported increases in tau phosphorylation related to greater Cdk5 activity, with changes in regulatory proteins MAPT and MAP-2, and increased oxidative stress, among other changes.

Effect of Cs on the tau protein

There are only a few studies on the effect of C pesticides on tau phosphorylation. It is important to highlight that there are no clinical or epidemiological studies on this topic, to date. Most of the studies analyzed in this review indicate that exposure to Cs led to hyperphosphorylation of tau[32,54,62,63]. Only two studies, reported otherwise[31,64]. Increased hyperphosphorylation may be mediated by increased GSK-3 β activity and PP2A inhibition (Table 3). In a murine model, exposure to carbofuran, a C pesticides resulted in neuronal death at the cortex and hippocampus, as well as alterations in spatial memory and learning processes[65]. It is interesting to note that C pesticides are currently being used for their therapeutic potential as AchE inhibitors in different pathologies[64,66,67]. More details associated with the effect of exposure to C pesticides on tau protein are presented in Table 3.

Effect of Ps on the tau protein

Exposure to P pesticides also increases tau protein phosphorylation by modifying the activity of kinase enzymes through over-activating. Contact with P pesticides is associated with increased immunoreactivity that affects cognitive processes, spatial memory, and learning, which are alterations consistent with the development of AD[32,65,68]. Three out the few studies that have been so far published on the effect of Ps on tau protein, and one review, are shown in Table 4. Amongst the most relevant results reported are increased activity of GSK-3 β [34,69], increased neuroinflammation[34,69] and decreased activity of PP2A[34].

Effect of Ns on the tau protein

Studies on the effect of N pesticides on tau protein in humans or experimental models are very few in number. The few reports available highlight the work of Kimura-Kuroda *et al*[70] who found that exposure to 1-100 μ M acetamiprid or imidacloprid (both N pesticides) increased intracellular Ca²⁺ influx in cerebellar neurons by activating calcium/calmodulin-dependent kinases, thereby over-stimulating tau protein phosphorylation. In a clinical case report on accidental ingestion of imidacloprid and thiamethoxam, the resultant increase in Ca²⁺ influx altered the kinase response [22]. Another mechanism involved activation of the Wnt pathway, leading to apoptosis[71]. More details are shown in Table 5.

PESTICIDES AND THEIR COGNITIVE IMPLICATIONS

Epidemiological studies have associated pesticide exposure with increased risks of cognitive impairment and AD[72,73]. For example, exposure to OC pesticides has been associated with low scores in the mini-mental test, and with severe cognitive decline[74-77]. Singh *et al*[78] reported that exposure to δ -hexachlorocyclohexane, dieldrin and pp'-dichlorodiphenyldichloroethylene were associated with AD (odds ratio = 2.064, 2.086 and 4.8, respectively; 95% confidence interval). These results are consistent with the cognitive findings[32-34,44,46-48,50,53,54,56,58,60,63,69,79] reported in Table 6, where contact with OCs was associated with increased cognitive impairment, decreased scores in tests evaluating spatial memory, decreased scores in results of tests on evaluation of novelty, and poor performance in tests evaluating attention and problem solving, except for two studies that did not report differences in scores in the tests applied[46,49].

Lin *et al*[80] reported that workers exposed to OPs had cognitive impairment (hazard ratio = 2.21; 95% confidence interval). Hayden *et al*[81] reported that exposure to OPs increased the risks of MCD and AD (hazard ratios = 1.38 and 1.42, respectively; 95% confidence interval), and Paul *et al*[82] reported that exposure to OPs has been associated with rapid progression to MCD (hazard ratio = 1.94, 95% confidence interval). In the studies analyzed in Table 6, it was found that contact with OPs was associated with decreased MMSE testing and deficiencies in tests involving evaluation of verbal, non-verbal and spatial memory (Table 6). These cognitive findings are related to the results presented by Lin *et al* [80], Hayden *et al*[81] and Paul *et al*[82] referred to above.

Table 3 Effects of carbamate pesticides on tau protein

Type of study	Sample	Type of pesticide	Exposure data	Tau phosphorylation	GSK-3 β	PP2A	Other mechanisms	Ref.
Experimental studies	C57BL/6 and 129/Sv mice	Maneb	Concentration: 30 mg/kg. Exposure time for 6 wk	Decreased	Decreased	NA	No changes in tau phosphorylation. However, if combined with paraquat, tau phosphorylation was enhanced in Ser202 (38% more), Ser262 (28% more) and Ser396/404 (141% more)	[31]
Experimental studies	Sprague-Dawley rats	Carbofuran	Concentration: 1 mg/kg. Exposure time of 28 d	Increased	Increased	Decreased	Increased phosphorylation of tau was observed in Ser198/199/202, Thr205 and Ser404. In addition, there was an increase in GSK-3 β and a decrease in PP2A	[32]
Experimental studies	NMRI mouse	Carbaryl	Concentrations: 0.5, 5.0, 20.0 mg/kg. Single dose	Increased	NA	NA	In the hippocampus, levels of phosphorylated tau increased by 135% in rats exposed to low, medium and high doses. In cerebral cortex, there was oscillating increase of 155% to 210% in tau phosphorylation	[54]
Experimental studies	Sprague-Dawley rats	Deltamethrin (P)/carbofuran (Cs)	Concentration: NA. Exposure time for 28 d	Increased	Increased	Decreased	Exposure induced tau hyperphosphorylation and GSK-3 β activation, as well as PP2A phosphatase inhibition	[63]
Review studies	Multiple studies	Cs	NA	Increased	Increased	NA	Exposure induced increased activity of kinase, thereby increasing phosphorylation of tau protein	[62]
Review studies	Multiple studies	Pyridine carbamate	Concentrations: 15.7 μ M. Single dose	Decreased	NA	NA	An inhibitory effect on phosphorylation was observed. This prevented the aggregation of tau protein	[64]

Ser: Serine; Thr: Treonine; GSK-3 β : Glycogen synthase kinase 3 beta; PP2A: Protein phosphatase-2A; NA: Not available; Cs: Carbamate; Ps: Pyrethroids.

Exposure to Cs is also associated with increased risk of developing MCD (odds ratio = 1.98; 95% confidence interval) [80]. Kamboj *et al* [83] showed that exposure of rats to Cs for 28 d performed poorly in Active Avoidance Task, indicating deterioration of cognitive function. Additionally, findings from studies on effect of Cs exposure on cognition have been linked to deterioration in spatial memory and decreased scores in results of tests involving evaluation of novelty (Table 6).

Very few studies have been done on the risk of cognitive impairment and AD due to exposure to P and N pesticides. In Taiwan workers exposed to Ns, approximately 2.9% mortality was reported, which is similar to the value of 3.1% reported for pyrethrins and Ps [22,79]. The results reported in Table 6 indicate that exposure to Ps is related to a deterioration in spatial memory, alteration in problem solving capacity, and increase in cognitive impairment similar to that reported by Estrada Atehortúa *et al* [22]. Besides, according to Phua *et al* [79], exposure to N pesticides resulted in aggravated disorientation, altered mental status, and confusion (Table 6).

Previously, the difficulty in studying the association between exposure to pesticides and prevalence of MCD and AD in humans was attributed to the complexity of obtaining separate data for each pesticide classification, because human exposure usually results from poisoning from multiple pesticides in conjunction with different chemical vehicles [65].

CONCLUSION

Pesticide exposure is associated with increased hyperphosphorylation of the tau protein amino acid residues Ser198, Ser199 and Ser202, Thr205, Ser396 and Ser404. This occurs through the following mechanisms: Increased enzyme activity of Cdk5 or GSK-3 β , decreased PPA2, mutations associated with the *MAPT* gene, increased neuroinflammatory response, enhanced influx of intracellular Ca²⁺, and impairment of oxidative phosphorylation. These mechanisms may be related to the pathogenesis of AD. In addition, exposure to pesticides may be involved in lower performance in mini-mental tests, alteration in verbal, non-verbal and spatial memory, decreased response to novelty tests, and reductions in attention and problem-solving potential. One limitation in this study is the small number of publications on Cs, Ps and Ns pesticides and their effects on tau protein. Therefore, there is need to carry out a broader study on these variables in subsequent investigations.

Table 4 Effects of pyrethroid pesticides on tau protein

Type of study	Sample	Type of pesticide	Exposure data	Tau phosphorylation	GSK-3 β	PP2A	Other mechanisms	Ref.
Experimental studies	Sprague-Dawley rats	Deltamethrin	Concentration: 12.5 mg/kg. Exposure time for 28 d	Increased	Increased	Decreased	Increased phosphorylation of tau was observed in Ser198/199/202, Thr205 and Ser404	[32]
Experimental studies	Wistar rats	Cyfluthrin, imiprothrin, prallethrin	Concentrations: 25%, 50% and 75%. Exposure time of 45 d	Increased	Increased	Decreased	Higher immunoreactivity of tau occurred in the hippocampus with high exposures to Ps. For medium and low doses, low immunoreactivity occurred. On the other hand, the activity of GSK-3 β was increased, while that of PP2A 2 was decreased	[34]
Experimental studies	Wistar rats	Cypermethrin	Concentration: 10 mg/kg and 25 mg/kg. Exposure time for 2, 3 and 6 wk	Increased	Increased	NA	In weaned exposed rats, tau phosphorylation increased in frontal cortex and hippocampus. This was induced by an increase in GSK-3 β activity. Furthermore, increased neuroinflammation was observed with increased production of IL-1 β	[69]
Review studies	Multiple studies	Ps	NA	Increased	Increased	NA	Exposure to Ps induced increased kinase activity, thereby increasing the phosphorylation of tau protein	[62]

Ps: Pyrethroid; IL: Interleukin; GSK-3 β : Glycogen synthase kinase 3 beta; PP2A: Protein phosphatase-2A; NA: Not available.

Table 5 Effects of neonicotinoid pesticides on tau protein

Type of study	Sample	Type of pesticide	Exposure data	Tau phosphorylation	GSK-3 β	PP2A	Other mechanisms	Ref.
Clinical/epidemiological studies. Clinical case	Accidental intake with Ns	Imidacloprid and thiamethoxam	Concentration: NA. Single dose	NA	NA	NA	The metabolite desnitro-imidacloprid activated the flow of intracellular calcium, thereby altering the response of kinase enzymes, and causing an excitatory neurological phase	[22]
Experimental studies	Primary cultures of cerebellar neurons from neonatal Sprague-Dawley rats	Acetamiprid imidacloprid	Concentrations: 1-100 μ M. Exposure time of 600 s	NA	NA	NA	Exposure to Ns increased the influx of Ca ²⁺ in cerebellar neurons. These pesticides excited cerebellar neurons to a degree similar to that from nicotine exposure. The influx of calcium ions activated the VDCC	[70]
Experimental studies	Human neural cells	Desnitro-imidacloprid	Concentration: 50 μ M. Exposure time of 48 h	Increased	Increased	Decreased	Activation of Wnt signal pathway. Exposure induced tau hyperphosphorylation by a GSK-3 β response, this enzyme is associated with Beta catenin activity. Exposure to this Ns induced watered-down expression that regulated tau hyperphosphorylation and apoptotic responses that impacted synaptotoxicity	[71]

Ns: Neonicotinoid; GSK-3 β : Glycogen synthase kinase 3 beta; PP2A: Protein phosphatase-2A; NA: Not available; VDCC: Voltage-dependent calcium channels.

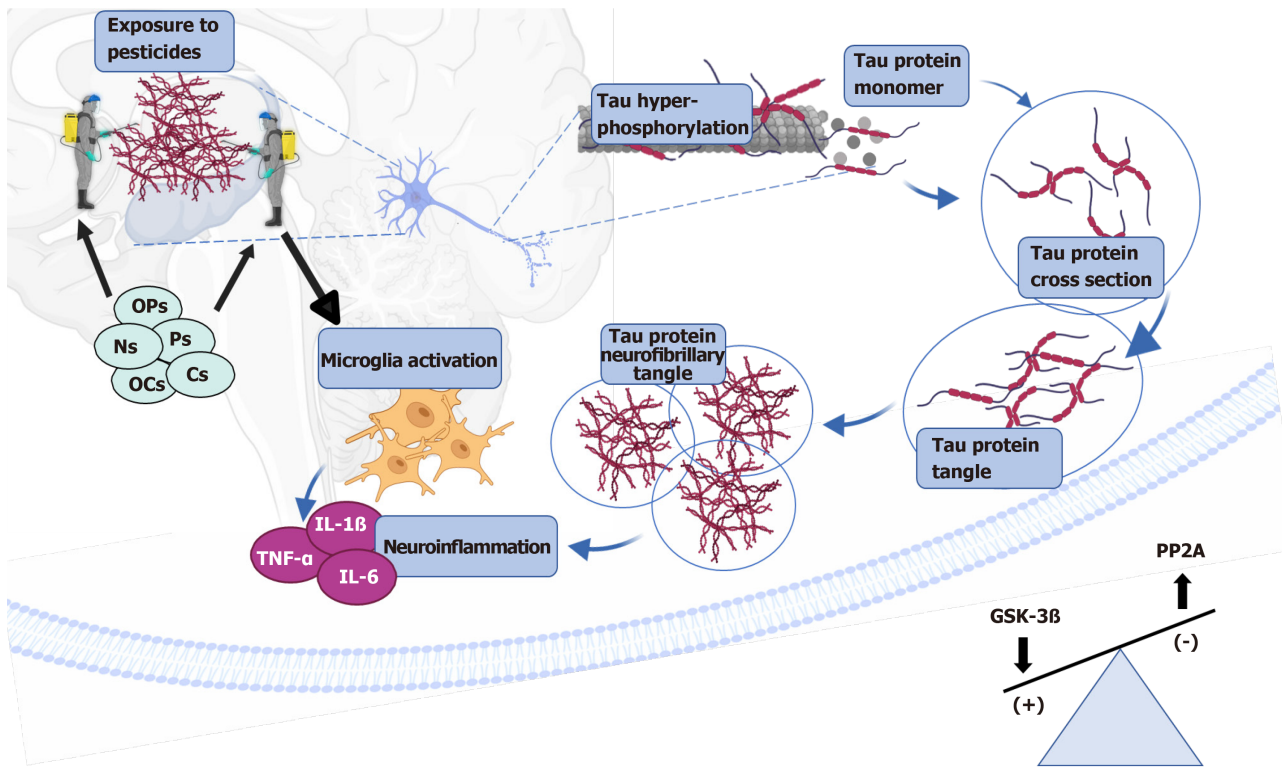
Table 6 Effect of pesticides on cognitive processes

Type of study	Sample	Type of pesticide	Exposure data	Cognitive implications	Ref.
Clinical/epidemiological studies. Cross-sectional	90 subjects with PD and 90 healthy subjects	OCs: δ -HCH	Concentration: NA. Exposure time NA	MMSE ¹ values in subjects with PD and without exposure to OCs: 27.66 ± 4.63 . MMSE ¹ values in healthy subjects with exposure to OCs: 24.33 ± 4.31	[45]
Clinical/epidemiological studies. Cohort	13 postmortem brains of subjects without exposure and 4 postmortem brains of subjects with exposure	OCs	Concentration: NA. Exposure time: from 0 to 10 yr	Last CASI ¹ score of subjects without exposure: 67.9 ± 24.4 . Last CASI ¹ score of subjects with exposure: 41.6 ± 22.8	[44]
Experimental studies	Strains of <i>Caenorhabditis elegans</i> (N2 BR5271)	OCs: DDT	Concentration: 3 μ M. Exposure time of 2 h	No significant differences reported in Associative Learning Paradigm tests	[46]
Experimental studies	Wistar rats	OCs: Chlordane	Range of concentration: 1 to 100 nM. Chronic exposure	Exposure did not affect results of tests that measured spatial memory	[49]
Review studies	Multiple studies	OCs: TCDD	Range of concentration: 5 to 23 ppt. Single dose	Decreased performance in verbal and nonverbal memory tests	[48]
Clinical/epidemiological studies. Cases and controls, unpaired	33 subjects exposed to OPs and 33 subjects without exposure	OPs	Concentration: NA. Exposure time 2 yr	87% of exposed subjects had cognitive impairment. Exposure to OPs for 10 yr increased the risk of cognitive decline 17 times	[53]
Experimental studies	Wistar rats	OPs: Chlorpyrifos-oxon	Range of concentration: 1 to 100 nM. Chronic exposure	Rats exposed to OPs showed deterioration of spatial memory	[49]
Experimental studies	NMRI mouse	OPs: Chlorpyrifos	Concentration: 0.1, 1.0, 5.0 mg/kg. Single dose	Decreased locomotion response and novelty were observed in rats exposed to this OPs	[54]
Experimental studies	Transgenic AD model rats	OPs: Chlorpyrifos	Concentrations: 3 and 10 mg/kg. Exposure time of 21 d	Exposure was associated with accelerated cognitive impairment in male rats, as indicated in memory and recognition tests	[50]
Experimental studies	Wistar rats	OPs: Malathion	Concentration: 100 mg/kg. Exposure time of 14 d	Decrease in spatial memory (evaluated using Morris water maze). This decrease was related to tau hyperphosphorylation	[33]
Experimental studies	Cell culture hiPSC and Wistar rats	OPs: DFP	Cell culture concentration: 200 nM. Exposure time for 2 d. Murine concentration: 1.5 mg/kg. Exposure time for 7 d	Slight decreases in learning and memory tests in the Morris water maze tests, and in 0 new object recognition	[56]
Review studies	Multiple studies	OPs	Different conditions	Lower performance in MMSE was associated with the exposure, with a modestly increased risk of MCD	[58]
Review studies	Multiple studies	OPs	NA	Exposure produced psychotic episodes, and alterations in attention, memory, problem solving, abstraction and cognitive flexibility	[59]
Review studies	Multiple studies	OPs ester	Different conditions	Decreased attention, visual memory, persistent and longer cognitive dysfunction and short-term memory	[60]
Experimental studies	Sprague-Dawley rats	Cs: Carbofuran	Concentration: 1 mg/kg. Exposure time of 28 d	Rats exposed to this pesticide took longer time to solve the Morris water maze, relative to the control group	[32]
Experimental studies	NMRI mouse	Cs: Carbaryl	Concentrations: 0.5, 5.0, 20.0 mg/kg. Single dose	Decreased locomotion response and response to novelty test in rats exposed to this pesticide	[54]
Experimental studies	Sprague-Dawley rats	Cs: Carbofuran	Concentration: NA. Exposure time for 28 d	Exposed rats had longer escape latency time in the Morris water maze test. Exposure was related to spatial memory deficit	[63]
Experimental studies	Sprague-Dawley rats	Ps: Deltamethrin	Concentration: 12.5 mg/kg. Exposure time for	Rats exposed to this pesticide took longer time to solve the Morris water maze,	[32]

			28 d	relative to the control group	
Experimental studies	Wistar rats	Ps: Cypermethrin	Concentration: 10 mg/kg and 25 mg/kg. Exposure time for 2, 3 and 6 wk	Cognitive impairment was induced; deficiencies in learning and memory of exposed rats occurred. These changes may be related to changes in calcium-dependent kinases and calmodulin	[69]
Experimental studies	Wistar rats	Ps: Cyfluthrin, Imiprothrin and Prallethrin	Concentrations: 25%, 50% and 75%. Exposure time of 45 d	Rats with the highest P exposure had higher cognitive impairment, when compared to control rats and other concentrations, possibly <i>via</i> increased activation of astrocytes in hippocampus	[34]
Clinical/epidemiological studies. Retrospective study of suicidal patients	Accidental intake of different Ns	Ns: Imidacloprid	Different concentrations. Single dose	Disorientation, altered mental status, lack of coordination and confusion	[79]

¹mean ± SD.

OCs: Organochlorines; OPs: Organophosphates; NA: Not available; DFP: Diisopropyl fluorophosphate; MMSE: Mini Mental State Examination; CASI: Cognitive Abilities Screening Instrument; Ps: Pyrethroids; Ns: Neonicotinoids; Cs: Carbamates; MCD: Major cognitive disorders; hiPSC: Human-induced pluripotent stem cells; δ -HCH: δ -hexachlorocyclohexane; DDT: Dichlorodiphenyltrichloroethane; AD: Alzheimer's disease; TCDD: 2,3,7,8 tetrachlorodibenzo-p-dioxin; PD: Parkinson disease.



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Figure 1 Pesticide effect on phosphorylation in tau. Exposure to pesticides organochlorine, organophosphate, carbamate, pyrethroid and neonicotinoid alters the balance of enzymatic activity of glycogen synthase kinase 3 beta (GSK-3 β) and protein phosphatase-2A (PP2A). Especially the increase of GSK-3 β and the decrease of PP2A favors tau hyperphosphorylation and the formation of neurofibrillary tangle which induce the activation of microglia and neuroinflammations. Created with Biorender.com. OCs: Organochlorine; OPs: Organophosphate; Cs: Carbamate; Ps: Pyrethroid; Ns: Neonicotinoid; GSK-3 β : Glycogen synthase kinase 3 beta; PP2A: Protein phosphatase-2A; TNF: Tumor necrosis factor; IL: Interleukin.

FOOTNOTES

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