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REVIEW ARTICLE

The susceptibility of humans to neurodegenerative and neurodevelopmental toxicities caused by organophosphorus pesticides

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Abstract

The toxicology field is concerned with the impact of organophosphorus (OP) compounds on human health. These compounds have been linked to an increased risk of neurological disorders, including neurodegenerative and neurodevelopmental diseases. This article aims to review studies on the role of OP compounds in developing these neurological disorders and explore how genetic variations can affect susceptibility to the neurotoxicity of these pesticides. Studies have shown that exposure to OP compounds can lead to the development of various neurological disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD), autism, intellectual disability, and other developmental neurotoxicities. Apart from inhibiting the cholinesterase enzyme, OP compounds are believed to cause other pathological mechanisms at both the extracellular level (cholinergic, serotonergic, dopaminergic, glutamatergic, and GABAergic synapses) and the intracellular level (oxidative stress, mitochondrial dysfunction, inflammation, autophagy, and apoptosis) that contribute to these disorders. Specific genetic polymorphisms, including PON1, ABCB1, NOS, DRD4, GST, CYP, and APOE, have increased the risk of developing OP-related neurological disorders.

Keywords Organophosphorus · Pesticides · Neurodegenerative · Neurodevelopmental · Alzheimer · Parkinson · Autism · ADHD · Polymorphism · Gene-environment

Introduction

OP compounds are a type of organic chemical that includes phosphorus. The origins of OP compounds date back to the 1930s when German scientists synthesized the first class of G-series nerve agents, such as Tabun, which have an OP chemical structure. Subsequently, other G-series nerve agents like Sarin, Soman, and Cyclosarin were introduced for use in chemical warfare. However, the production, stockpiling, and use of these chemical warfare agents have been prohibited by nations under the Chemical Weapons Convention (CWC). Despite this, OP compounds are widely used in other industries, such as flame retardants, plasticizers, engine oil additives, medicines, and pesticides. The extensive use of OP compounds as insecticides and herbicides in agricultural fields, crop development, gardening, animal husbandry, and household applications has resulted in the inevitable exposure of humans to these chemicals (Abdollahi and Mostafalou 2014a). Biochemically, OP compounds inhibit acetylcholinesterase (AChE), an enzyme responsible for the hydrolysis of the neurotransmitter acetylcholine in different parts of the nervous system. This inhibition can lead to the accumulation of acetylcholine in the synapses and overstimulation of postsynaptic neurons, causing death in insects or neurotoxicity in non-target organisms (Abdollahi and Mostafalou 2014b). Long-term and low-level exposure to OP compounds has been linked to higher human health problems, including neurological, metabolic, and reproductive disorders. These chemicals disrupt the elements of the nervous system, which has led to extensive research on their potential neurotoxicity, focusing on different pathophysiological aspects like neuropathy, neurodegenerative

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and neurodevelopmental toxicity (Mostafalou and Abdollahi 2013; Mostafalou and Abdollahi 2017). In recent decades, environmental toxicologists have focused on studying neurodevelopmental disorders like attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), and intellectual disabilities. OP compounds have been found to significantly impact the development of these disorders, as evidenced by numerous studies (Arab and Mostafalou 2022; Mostafalou and Abdollahi 2018).

This article thoroughly reviews the research linking OP compounds to neurodegenerative diseases like Parkinson's and Alzheimer's and neurodevelopmental diseases such as ADHD, ASD, and other related disabilities. We will discuss how OPs can be toxic to the nerves and lead to different disorders. Also, we will be looking into why there is an increase in neurological disorders and how genetic vulnerabilities can strengthen neurotoxic mechanisms.

Methods

We searched for research articles on the connection between exposure to OP compounds and neurodevelopmental and neurodegenerative disorders using PubMed. Our search spanned from 1980 to 2023, and we limited our selection to papers published in English.

Literature search

The search used specific keywords to find epidemiological evidence connecting OP compounds to neurodegenerative and neurodevelopmental disorders. These keywords included "organophosphorus," "neurodegenerative disorders", "neurodevelopmental disorders," "Alzheimer's," "Parkinson's," "attention deficit hyperactivity disorder (ADHD)," "autism," and "intellectual disability."

For pathological mechanisms involved in OP-induced neurotoxicity, the search was concluded from a separate combination of keywords including "organophosphorus" and the following words: "neurodegenerative disorders," "neurodevelopmental disorders," "cholinesterase," "synaptic dysfunction," "oxidative stress," "mitochondrial dysfunction," "inflammation," "autophagy," and "apoptosis."

For the role of genetic polymorphism in the susceptibility to OP-induced neurological disorders, the search was concluded from a separate combination of keywords including "organophosphorus" and the following words: "neurodegenerative disorders," "neurodevelopmental disorders," "polymorphism," "single nucleotide polymorphism" and "gene-environment."

Inclusion/ exclusion criteria

All related epidemiological studies evaluating the association of OP compounds with human neurodegenerative and neurodevelopmental disorders were selected based on their title, abstract, and if needed, full text. The included articles had the following criteria:

- Sample size
- Type of diseases: Parkinson's, Alzheimer's, ADHD, autism, intellectual disability.
- Exposure assessment tool: questionnaire, interview, geographic information system, chemical analyses of blood, urine, and other biological samples.
- Type of OP compounds or OP metabolites.
- Types of outcome measures: association or no association between OP exposure and neurodegenerative and neurodevelopmental disorders.

Data extraction

After the classification of disorders based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V), the following information was extracted from selected papers and entered in related tables:

- Author's name
- Publication date
- Sample descriptions
- Exposure assessment tools include interviews, questionnaires, geographic information systems (GIS), and biological fluid levels of pesticides or their metabolites.

Results

After searching in PubMed, a total of 9122 records were found. These records were screened by looking at their titles, abstracts, and full texts to eliminate irrelevant ones. The number of articles reviewed for each part of the search was as follows: 64 for epidemiological evidence on the connection between OP compounds and neurodegenerative and neurodevelopmental disorders, 62 for experimental evidence on the role of OP compounds in the development of these disorders, and 22 for genetic polymorphisms related to susceptibility to OP-induced neurodegenerative and neurodevelopmental disorders (see Fig. 1).

Numerous epidemiological studies have explored the connection between OP compounds and neurodegenerative and neurodevelopmental disorders. Table 1 contains the

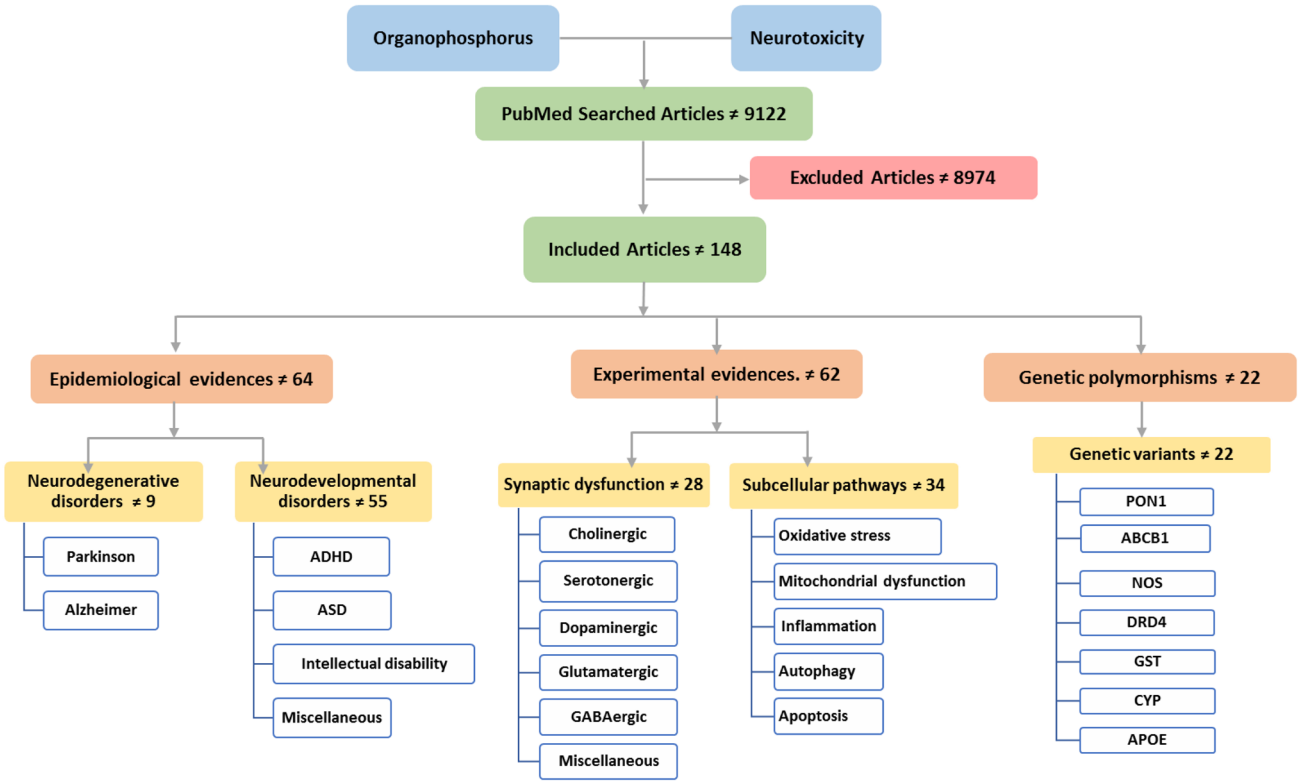

Fig. 1 A schematic flow chart indicating the types of literature searches and the number of articles included and excluded in the systematic review

findings of 9 studies on neurodegenerative disorders and 55 studies on neurodevelopmental disorders.

Parkinson's disease

Parkinson's disease (PD) is a type of neurodegenerative disorder that affects the motor functions of the central nervous system. This disease is the second most common neurological illness that affects older individuals and progressively worsens over time. Previous research studies have shown that people exposed to pesticides, whether occupationally or environmentally, are at a higher risk of developing PD. This study presents the results of six epidemiological studies that evaluate the correlation between exposure to OPs and PD. Dhillon and his colleagues found an increased odd ratio (OR) of 2 among people exposed to chlorpyrifos, as evaluated by self-reporting environmental and occupational exposures (Dhillon et al. 2008).

Additionally, two other population-based case-control (CC) studies conducted by Narayan and his colleagues evaluated the effects of household and occupational use of OP pesticides on the risk of PD. According to their results, the risk of developing PD increased by 71% and 100%, respectively (Narayan et al. 2017; Narayan et al. 2013). According to a cross-sectional (CS) study utilizing a geographic information system (GIS)-based model, exposure to chlorpyrifos resulted in an 87% increase in the relative risk of PD (Gatto et al. 2009). Another GIS-based CS study found carriers of a functional polymorphism at position 55 of the PON1 gene exposed to chlorpyrifos and diazinon had over a 2-fold increase in the risk of PD compared to those with a wild-type genotype and no exposure (Manthripragada et al. 2010). Furthermore, a GIS-based cohort study monitored 246 incident PD patients for an average of 5 years and found that high OP exposures were linked to faster progression of motor and cognitive scores. Additionally, the interaction of PON1 L55M variants with OP exposure influenced cognitive scores (Paul et al. 2017).

Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia. AD affects parts of the brain controlling thought, memory, learning, and organizing skills. There has been some evidence of the link between pesticide exposure and the risk of AD. However, the study of Hayden and his colleagues has been the most comprehensive epidemiological project on this subject. They followed the cognitive status of 3084 residents of an agricultural area over ten years. They found

Table 1 Studies associating OP pesticide exposure with neurodegenerative and neurodevelopmental disorders and the main findings

Study	Sample size	Exposure assessment	OP or OP metabolite	The main findings
Dhillon et al. (2008)	100/84	Questionnaire	Chlorpyrifos	↑ risk of PD
Gatto et al. (2009)	368/341	GIS	Chlorpyrifos	↑ relative risk of PD
Manthripragada et al. (2010)	351/363	GIS	Diazinon, chlorpyrifos	↑ risk of PD in PON1-55 variant carriers
Narayan et al. (2013)	357/807	Interview	OPs, Chlorpyrifos	↑ risk of PD with household use
Narayan et al. (2017)	360/827	Interview	OPs	↑ risk of PD with occupational exposure
Paul et al. (2016)	357/495	GIS	OPs	↑ risk of PD in NOS1 variant genotypes
Paul et al. (2017)	246	GIS	OPs	↑ progression of motor and cognitive score in PD patients
Hayden et al. 2010	3084	Questionnaire	OPs	↑ hazard ratio of AD
Paul et al. (2018)	430	GIS	OPs	↓ cognitive ability in elderly
Bouchard et al. (2010)	1139	Urine analysis	DAPs	↑ risk of ADHD in children 8-15 years old
Marks et al. (2010)	323	Urine analysis	DAPs	↑ risk of ADHD in children 5 years
Fortenberry et al. (2014)	187	Urine analysis	Chlorpyrifos	↑ risk of ADHD in children 6-11 years
Van Wendel De Joode et al. (2016)	140	Urine analysis	Chlorpyrifos	↑ risk of ADHD in children 6-9 years
Yu et al. (2016)	97/110	Urine analysis	DAPs	↑ risk of ADHD in children 4-15 years
Chang et al. (2018)	93/112	Blood analysis	DAPs	↑ risk of ADHD in children with DRD4 gene polymorphism
Rohlman et al. (2019)	64	Urine analysis	Chlorpyrifos metabolite	↑ risk of ADHD in adolescents
Dalsager et al. (2019)	948	Urine analysis	Chlorpyrifos	↑ risk of ADHD in children 1.5-5 years
Van den Dries et al. (2019)	784	Urine analysis	DAPs	No association with ADHD
Chang et al. (2021)	85/96	Urine analysis	DAPs	↑ risk of ADHD in children
Choi et al. (2021)	295/555	Urine analysis	OPE metabolites	↑ risk of ADHD in children
Sagiv et al. (2021)	351	Urine analysis	DAPs	↑ risk of ADHD in children 7-12 years
Waits et al. (2022)	76/98	Urine analysis	DAPs	↑ risk of ADHD in children 4-15 years
Hall et al. (2023)	260/549	Urine analysis	OPE metabolites	↑ risk of ADHD in preschool children
Eadeh et al. (2023)	226	Urine analysis	Chlorpyrifos metabolite	No association with ADHD in adolescent males
D'Amelio et al. (2005)	284	Indirect in vitro	Diazinon	↑ risk of ASD in carriers of PON1 Q192R
Shelton et al. (2014)	486/316	GIS	OPs, Chlorpyrifos	↑ risk of ASD
Philippat et al. (2018)	203	Urine analysis	DMTP	↑ risk of ASD in girls 3 years old
Sagiv et al. (2018)	601	Urine analysis	DAPs	No association with ASD
Von Ehrenstein et al. (2019)	2961/35370	GIS	Glyphosate, Chlorpyrifos, Diazinon, Malathion	↑ risk of ASD
Van den Dries et al. (2019)	622	Urine analysis	DAPs	No association with ASD
Lizé et al. (2022)	792	Urine analysis	Chlorpyrifos	↑ risk of ASD in children 11 years
Ruckart et al. (2004)	132/147	Urine analysis	Methyl parathion	↓ short-term memory and attention at first 6 years ↑ behavioral and motor skill problems in the first 6 years
Engel et al. (2011)	360	Urine analysis	DAPs	↓ cognitive development at first 6-year ↑ effect in carriers of PON1 Q192R
Bouchard et al. (2011)	329	Urine analysis	DAPs	↓ intellectual development in children 7 years
Stein et al. (2016)	329	Urine analysis	DAPs	↓ cognitive ability at first 7 year
Donauer et al. (2016)	327	Urine analysis	DAPs	No association with cognition at 1-5 years
Gunier et al. (2017)	283	Urine analysis	DAPs	↓ full-scale IQ in children 7 years
Kongtip et al. (2017)	50	Urine analysis	DAPs	↓ cognitive & motor development at 5 months
Ntantu et al. (2020)	607	Urine analysis	DAPs	↓ cognitive ability in children 3-4 years ↓ verbal IQ in boys
Rauh et al. (2011)	265	Cord blood analysis	Chlorpyrifos	↓ Working Memory Index in children 7 years ↓ full-scale IQ in children 7 years

Table 1 (continued)

Study	Sample size	Exposure assessment	OP or OP metabolite	The main findings
Doherty et al. (2019a, b)	149	Urine analysis	OPE metabolites	↓ cognitive ability in children 2-3 years
Percy et al. (2022)	223	Urine analysis	OPE metabolites	↓ cognitive abilities at 8 years
Butler-Dawson et al. (2016)	206	Home residue	OPs	↓ learning ability in school-aged children
Young et al. (2005)	381	Urine analysis	DAPs	No association with neurobehavioral development in neonates < or = 2 months
Grandjean et al. (2006)	37/35	Urine analysis	DAPs	↑ reaction time in children < 9 years
Rauh et al. (2006)	254	Cord blood analysis	Chlorpyrifos	↓ psychomotor Development Index at first 3-year ↓ mental Development Index at first 3-year
Eskenazi et al. (2007)	372	Urine analysis	DAPs	↓ mental & pervasive development in children 2 years
Rauh et al. (2012)	20/20	Cord blood analysis	Chlorpyrifos	Structural change in brain development of children 6-11 years
Guodong et al. (2012)	301	Urine analysis	DAPs	No association with neurodevelopment in children 2 years
Yolton et al. (2013)	350	Urine analysis	DAPs	No neurobehavioral effects in infants at 5 weeks
Furlong et al. (2014)	136	Urine analysis	DAPs	↓ social functioning in blacks & boys at 7-9 years
Zhang et al. (2014)	249	Urine analysis	DAPs	↓ neurobehavioral development in neonates
Naksen et al. (2015)	52	Urine analysis	DAPs	↓ birth weight and head perimeter in newborns of mother with lower PON1 activity
Engel et al. (2016)	936	Urine analysis	DAPs	↓ mental development indices in children 2 years and carriers of the 192Q PON1 allele
Wang et al. (2017)	436	Urine analysis	DAPs	↓ developmental indices in children 2 years
Woskie et al. (2017)	82	Urine analysis	DAPs	↑ abnormal reflexes in neonates
Millenson et al. (2017)	224	Urine analysis	DAPs	No association with social behavior in 8-years old children
Juntarawijit et al. (2020)	442/413	Interview	Chlorpyrifos	↑ developmental delay at first 5 year
Doherty et al. (2019a, b)	199	Urine analysis	OPE metabolites	↓ neurobehavioral development at 3 years
Rothlein et al. (2006)	96/45	Urine analysis	DAPs	↓ neurobehavioral performance in farmworkers
Mackenzie Ross et al. (2010)	127/78	Interview	OPs	↓ neurobehavioral performance in sheep farmers
Starks et al. (2012)	701	Interview	OPs	No association with neurobehavioral performance in adults
Berent et al. (2014)	113	Urine analysis	Chlorpyrifos	No association with neurobehavioral performance in adults
Ismail et al. (2017)	84	Urine analysis	Chlorpyrifos	↓ neurobehavioral performance in adolescents

GIS geographic information system, *OP* organophosphorus, *DAP* dialkyl phosphate, *OPE* organophosphate ester, *DMTP* dimethylthiophosphate, *PD* Parkinson's disease, *AD* Alzheimer's disease, *ADHD* Attention Deficit Hyperactivity Disorder, *DRD4* dopamine receptor D4, *ASD* autism spectrum disorders, *PON1* paraoxonase 1

that people with a history of occupational exposure to OP pesticides had a 53% higher risk of AD in late life (Hayden et al. 2010). Another epidemiological study on the aging population estimated ambient exposure to OP pesticides with a GIS-based tool. Participants with higher OP exposure experienced faster cognitive decline and higher mortality over follow-up (Paul et al. 2018).

Attention deficit hyperactivity disorder (ADHD)

ADHD is one of the main neurodevelopmental disorders affecting children and can continue until adulthood. Affected patients have trouble controlling their behaviors, and the main symptoms are hyperactivity, difficulty with attention, low self-esteem, and troubled relationships. During the last

two decades, many epidemiological studies have evaluated the relationship of pesticide exposure with a higher incidence of ADHD in children and adolescents. In this work, we reviewed the results of 14 epidemiological pieces of evidence on the relationship between OPs and the incidence of ADHD in children. Seven of these studies assessed OP exposure via analyzing the dialkyl phosphate (DAP) metabolites in urine samples, and except for one study with a sample size of 784 (van den Dries et al. 2019), the other studies with a total sample size of 2375 reported that exposure to OP compounds was associated with a higher incidence of ADHD in children (Bouchard et al. 2010; Chang et al. 2021; Marks et al. 2010; Sagiv et al. 2021; Waits et al. 2022; Yu et al. 2016). Change and colleagues have also evaluated the link of ADHD with OP exposure by analyzing DAP metabolites in the blood and found that OP exposure caused an increase in the risk of ADHD in children with dopamine receptor D4 gene polymorphism (Chang et al. 2018). Four epidemiological studies with a total sample size of 1339 analyzing chlorpyrifos of chlorpyrifos metabolites in the urine reported that exposure to chlorpyrifos was associated with a higher incidence of ADHD in children and adolescents (Dalsager et al. 2019; Fortenberry et al. 2014; Rohlman et al. 2019; van Wendel de Joode et al. 2016). Organophosphate esters (OPE) have also been chemically related to OP compounds commonly used as flame retardants. Two studies with a total sample size of 1659 evaluated the level of OPE metabolites in the urine and reported that higher exposure to OPEs was associated with an increased risk of ADHD in children (Choi et al. 2021; Hall et al. 2023).

Autism spectrum disorder (ASD)

ASD is a neurodevelopmental disorder that can manifest differently in each patient. The most common characteristics of ASD include disability in social communication and repetitive or limited patterns of behaviors or interests. During the last two decades, some epidemiological studies have reported a link between exposure to environmental pollutants like pesticides and a higher incidence of ASD in children. D'Amelio and colleagues evaluated the link of OP exposure with the risk of ASD indirectly. They reported a significant association between autism and genetic polymorphism of PON1, Q192R, which was less active in vitro on the OP diazinon (D'Amelio et al. 2005). The results of the Childhood Autism Risks from Genetics and Environment (CHARGE) study conducted on 486 ASD cases and 316 controls showed that proximity to the areas of OP pesticide applications, particularly chlorpyrifos during gestation, was associated with a 60% increased risk for ASD in children (Shelton et al. 2014). Another population-based case-control study conducted on birth data of 2961 ASD cases and 35370 controls evaluated OP exposure by a geographic information system (GIS) tool and reported that the risk of ASD was increased following prenatal exposure to glyphosate, chlorpyrifos, diazinon, and malathion (von Ehrenstein et al. 2019).

Four separate studies have examined the presence of OP metabolites in urine samples from mothers of children diagnosed with ASD. One such study, conducted by Philippat and colleagues, discovered that there was an elevated risk of ASD in girls whose mothers had higher concentrations of OP metabolites, but this correlation was not observed in boys until the data was examined by sex (Philippat et al. 2018). According to a recent study by Lizé et al. (2022), prenatal exposure to chlorpyrifos and possibly diazinon may increase autistic traits in 11-year-old children, as indicated by the evaluation of OP metabolites. However, no significant association was found for DAPs, terbufos, and its metabolites. Two other studies are currently investigating the link between maternal urinary concentration of OP metabolites and autistic traits in children. Sagiv et al. (2018) and van den Dries et al. (2019) found no strong association between prenatal exposure to OP metabolites and ASD.

Intellectual disability (ID)

ID is a neurodevelopmental disorder formerly known as mental retardation and characterized by deficits in cognitive functioning and adaptive behaviors. There are various classifications for ID, such as mild, moderate, and severe, or syndromic and non-syndromic. The causes of ID may be genetic inheritance or any environmental exposures affecting brain development. The intelligence quotient (IQ) test is widely used to diagnose ID. Nevertheless, mild ID may only be identified at school age in children. Various studies have shown that pesticide exposure, particularly in prenatal and postnatal stages, is associated with a higher incidence of ID in children. Herein, the results of 12 epidemiological studies on the relation of exposure to OPs with the risk of ID have been reviewed. The first study relates to the association between methyl parathion exposure and neurobehavioral development. The authors of the study indicated that their findings were inconclusive. However, they did identify a correlation between elevated levels of methyl parathion in urine and certain issues in children under six years old. These issues included slight impairments in short-term memory and attention, as well as difficulties with motor skills and behavior. (Ruckart et al. 2004). Engel and colleagues analyzed the relationship between the urinary concentrations of DAPs in mothers and cognitive development in children at their first six years of age. They concluded that prenatal exposure to OPs was associated with decreased cognitive development, particularly perceptual reasoning, and the association appeared to be enhanced among children of mothers

who carried the PON1 Q192R QR/RR genotype (Engel et al. 2011). The results of three studies conducted on the same population indicated that prenatal exposure to OPs assessed by the urinary concentration of DAPs in mothers was significantly associated with decreased intellectual development, cognitive ability, and full-scale IQ in 7-year-old children (Bouchard et al. 2011; Gunier et al. 2017; Stein et al. 2016). Three more studies evaluate the effect of prenatal exposure to OPs by analyzing the urinary concentration of DAPs in mothers. Except one, the other two studies reported decreased cognitive and motor development in offspring at 5 months of age and lower cognitive ability and verbal IQ in 3–4-year-old children, respectively (Donauer et al. 2016; Kongtip et al. 2017; Ntantu Nkinsa et al. 2020). Rauh and colleagues monitored the neurodevelopmental effects of prenatal exposure to chlorpyrifos assessed by umbilical cord blood analyses in an ongoing prospective cohort study conducted on children between 1 and 11 years of age.

The first report found that prenatal exposure to chlorpyrifos was associated with Psychomotor Development Index and Mental Development Index delays, attention problems, ADHD-related problems, and pervasive developmental disorders during the first three years of age (Rauh et al. 2006). Their second report indicated that higher levels of chlorpyrifos in cord blood were associated with decreased Working Memory Index and Full-Scale IQ in 7-year-old children (Rauh et al. 2011). Finally, they compared the brain morphology of 20 high-exposure children (determined by upper tertile of chlorpyrifos concentration in umbilical cord blood) with that of 20 low-exposure children aged 6-11 years old using magnetic resonance imaging. They concluded that prenatal exposure to chlorpyrifos increased the risk of structural changes in the developing brain, such as frontal and parietal cortical thinning (Rauh et al. 2012). The deficit in neurobehavioral performance of 206 school-aged children evidenced by decreased learning ability was reported to be associated with a higher concentration of OP residues in their home carpet dust samples (Butler-Dawson et al. 2016). Doherty and colleagues also studied the cognitive effects of prenatal exposure to OPEs. They reported that higher urinary concentrations of OPE metabolites in mothers were adversely associated with cognitive development, including fine motor skills and early language abilities in children between two and three years of age (Doherty et al. 2019b). There is another study evaluated the relation of urinary concentration of OPE metabolites in children ages 1–5 years with cognitive abilities at eight years and reported a decrease in full-scale IQ in children with higher exposure and among those with lower maternal education, non-white race, and lower-income (Percy et al. 2022). Butler-Dawson and colleagues reported that school-aged children with higher exposure to OPs, assessed by parent's occupation and OP residues in-home carpet dust samples, had lower learning ability (Butler-Dawson et al. 2016).

Other neurodevelopmental and neurobehavioral disabilities

The results of 12 studies evaluating the relation of urinary concentration of DAPs in mothers with neurodevelopmental and neurobehavioral disabilities have been reviewed. Four of them did not find any association between prenatal exposure to OPs and neurobehavioral and neurodevelopmental effects in children at the age of 5 weeks, two months, and two years, respectively (Guodong et al. 2012; Millenson et al. 2017; Yolton et al. 2013; Young et al. 2005). Two studies conducted on neonatal neurodevelopment assessed by Neonatal Behavioral Neurological Assessment (NBNA) and Brazelton Neonatal Behavioral The Neonatal Behavioral Assessment Scale (NBAS) revealed that exposure to OPs during pregnancy increases the risk of lower neurobehavioral development scores and higher abnormal reflexes in newborns (Woskie et al. 2017; Zhang et al. 2014). Three other studies evaluating the neurodevelopmental effects of prenatal exposure to OP among 2-year-old children reported a significant association between maternal urinary concentrations of DAPs and decreased mental and pervasive development indices. The study by Engel and colleagues reported that this effect was more significant in children of mothers who were the carrier of the 192Q PON1 allele (Engel et al. 2016; Eskenazi et al. 2007; Wang et al. 2017). Increased reaction time and social functioning problems in children younger than 9 years old were linked with a higher maternal urinary concentration of DAPs (Furlong et al. 2014; Grandjean et al. 2006). Naksen and colleagues evaluated the effects of prenatal exposure to OPs on fetal development and birth outcomes. They reported an association between maternal urinary concentration of DAPs and lower birth weight and head perimeter in newborns, and the association was more significant in newborns of mothers with a lower PON1 activity (Naksen et al. 2015). An interview-based case-control study evaluating the risk factors of developmental delay in children found that exposure to chlorpyrifos during pregnancy was positively associated with developmental delay in children under the age of 5 years (Juntarawijit et al. 2020). Prenatal exposure to OPEs has also been shown to decrease neurobehavioral development indices in children at age 3 by a prospective birth cohort study (Doherty et al. 2019a). There have been five studies conducted to investigate the harmful effects of exposure to OP compounds on the neurobehavioral performance of adults. Out of these studies, two found no correlation between exposure and poor performance (Berent et al. 2014; Starks et al. 2012), while the other three, which measured exposure through urine analysis and interviews, found that OP compounds could reduce

neurobehavioral performance among farmworkers and sheep farmers (Ismail et al. 2017; Mackenzie Ross et al. 2010; Rothlein et al. 2006).

Discussion

Inhibition of cholinesterase (ChE) enzymes by OP compounds

Enzymes known as ChE play a significant role in breaking down choline esters, which act as neurotransmitters in the nervous system. Acetylcholine, a crucial neurotransmitter present in cholinergic synapses, is terminated by the enzyme acetylcholinesterase (AChE). AChE is primarily expressed in the nervous system and red blood cells, while the other type of ChE, butyrylcholinesterase (BChE), is mainly present in the blood plasma. OP compounds, carbamates, and medications for treating myasthenia gravis, glaucoma, and AD act by inhibiting ChE enzymes. Inhibition of ChE enzymes leads to the accumulation of acetylcholine and overstimulation of cholinergic synapses. While there have been suggestions of alternative mechanisms that could contribute to the toxic effects of OP compounds during prolonged exposure, the inhibition of cholinesterase (ChE) enzymes remains the most widely accepted primary mechanism. This phenomenon explains the majority of adverse reactions associated with OP compounds. (Abdollahi et al. 2004; Mostafalou et al. 2012).

Synaptic dysfunctions involved in OP-induced neurotoxicity

When neurons communicate, they do so through intracellular clefts called CNS Synapses. These synapses transmit action-potential encoded information, and the proper establishment of these connections is crucial for normal nervous system function. Recent studies have shown that there is a relationship between disturbances in synaptic proteins and neurological diseases such as neurodegenerative and neurodevelopmental disorders (Lepeta et al. 2016; Taoufik et al. 2018). OP compounds, which are commonly found in pesticides, can cause toxicity by inhibiting the AChE enzyme that regulates the synaptic concentration of the ACh neurotransmitter in cholinergic neurons. However, there are other synaptic disturbances caused by OP compounds, even in the absence of AChE inhibition. Table 2 provides a summary of reports on these synaptic dysfunctions induced by OP compounds in experimental setups. These dysfunctions affect various types of synapses, including cholinergic, serotonergic, dopaminergic, glutamatergic, GABAergic, and miscellaneous.

Cholinergic transmission

Five in vivo studies evaluating cholinergic synaptic function reported that neonatal exposure of rats or mice to OP compounds could change the activity or expression of synaptic proteins like choline acetyltransferase (CAT), presynaptic choline transporters (CHT) and nicotinic ACh receptors (nAChR) and in adulthood. These changes were shown to be induced in brain regions, including ACh projecting regions, striatum, substantia nigra, hippocampus, and cerebral cortex under the effect of OP pesticides such as parathion, methyl parathion, and chlorpyrifos (Eells and Brown 2009; Levin et al. 2010; Ribeiro-Carvalho et al. 2020; Slotkin et al. 2008; Slotkin et al. 2009a). Subchronic exposure to dichlorvos at doses not changing AChE activity was also shown to cause neurobehavioral impairments and decrease muscarinic ACh receptor (m2AChR) level, ACh receptor signaling, and phosphorylation of cAMP response element-binding protein (CREB) in the brain of rats (Verma et al. 2009). An in vitro study conducted on SN56 basal forebrain cholinergic neurons indicated that acute and long-term exposure to chlorpyrifos could impair cholinergic transmission and increase CHT expression, most probably due to inhibition of the AChE activity. Another study finding was basal forebrain neuronal loss independent of AChE inhibition under acute and chronic effects of chlorpyrifos (del Pino et al. 2015).

Serotonergic transmission

Five studies investigating serotonergic synaptic functions in vivo reported that neonatal exposure of rats or mice to OP pesticides such as parathion and chlorpyrifos caused alterations in the level of 5HT transporters, 5HT receptors, 5HT turnover, and binding affinity of 5HT receptors and transporters in brain regions including basal forebrain, brainstem, hippocampus, cerebral cortex and some other ACh and 5HT projecting regions of adult animals (Levin et al. 2010; Raines et al. 2001; Ribeiro-Carvalho et al. 2020; Slotkin et al. 2009b; Slotkin et al. 2009c). An in vivo study has also shown that exposure to methamidophos in adulthood could alter the binding affinity of 5HT transporters and receptors in 5HT-producing brain regions in adult mice (Lima et al. 2011). An in vitro study using PC12 cells originating from rat adrenal medulla reported that exposure to chlorpyrifos and diazinon could increase the expression of tryptophan hydroxylase, which is a rate-limiting enzyme in 5HT biosynthesis and suppress the expression of 5HT transporters. Although the net effect would tend to enhance the extracellular concentration of 5HT, the effect of two OP compounds on the 5HT receptors had variations, so chlorpyrifos increased. At the same time, diazinon decreased the expression of most 5HT receptors (Slotkin and Seidler 2008).

Table 2 OP-induced synaptic dysfunctions in different brain regions evidenced by experimental studies *in vitro* and *in vivo*

Cholinergic synapses	OP	Type of study	Sample	Brain region	The main findings
Slotkin et al. (2008)	Parathion	In vivo	Neonatal rats	ACh projecting regions[a]	Altered CAT, nAChR and CHT
Slotkin et al. (2009a, b, c)	Parathion	In vivo	Neonatal rats	ACh projecting regions	Altered CAT, nAChR, and hemicholinium-3 binding
Verma et al. (2009)	Dichlorvos	In vivo	Rat	Whole brain	↓ ACh M_2 receptor, ACh pathway and CREB phosphorylation
Eells et al. (2009)	Chlorpyrifos Methyl parathion	In vivo	Neonatal rat	Striatum, substantia nigra	Altered expression of nAChR subtypes
Levin et al. (2010)	Parathion	In vivo	Neonatal rat	Hippocampus	Cognitive dysfunction ↓ CAT and nAChR
del Pino et al. (2015)	Chlorpyrifos	In vitro	Murine	Basal forebrain	↓ cholinergic transmission and AChE ↑CHT
Ribeiro-Carvalho et al. (2020)	Chlorpyrifos	In vivo	Neonatal mice	Cerebral cortex	↓ CAT activity and CHT
Serotonergic synapses					
Raines et al. (2001)	Chlorpyrifos	In vivo	Neonatal rats	Forebrain and brainstem	↓ 5HT transporter
Slotkin et al. (2008)	Chlorpyrifos Diazinon	In vitro	Rats	Adrenal medulla	↑ 5HT biosynthesis, ↓ 5HT transporter
Slotkin et al. (2009a, b, c)	Parathion	In vivo	Neonatal rats	5HT projecting regions [b]	↑ $5HT1_A$ receptors
Slotkin et al. (2009a, b, c)	Parathion	In vivo	Neonatal rats	ACh/5HT projecting regions	↑ turnover of 5HT, ↑5HT receptors
Levin et al. (2010)	Parathion	In vivo	Neonatal rats	Hippocampus	Cognitive dysfunction ↑5HT receptors and transporters
Lima et al. (2011)	Methamidophos	In vivo	Mice	5HT projecting regions	Altered binding of 5HT receptors and transporters
Ribeiro-Carvalho et al. (2020)	Chlorpyrifos	In vivo	Neonatal mice	Cerebral cortex	↓ binding of 5HT receptors and transporters
Dopaminergic synapses					
Eells et al. (2009)	Chlorpyrifos	In vivo	Neonatal rats	Striatum, substantia nigra	↑ DOPAC and DA turnover
Slotkin et al. (2009a, b, c)	Parathion	In vivo	Neonatal rats	ACh/5HT projecting regions	↑ turnover of DA
Torres-Altoro et al. (2011)	Chlorpyrifos	In vivo	Mouse	Striatum	↑ PKA dependent phosphorylation of DARPP-32
Faro et al. (2018)	Paraoxon	In vivo	Rats	Striatum	↑DA release due to AChE inhibition
Glutamatergic synapses					
Torres-Altoro et al. (2011)	Chlorpyrifos	In vivo	Mouse	Striatum	↑ GluR1 and PKA dependent phosphorylation of GluR1
Moyano et al. (2018)	Chlorpyrifos	In vitro	Murine	Basal forebrain	↑Glut, glutaminase activity, VGLUT1 ↑ GSK-3β, Aβ and phosphorylated tau proteins
Brown et al. (2020)	DFP	In vitro	Mouse	Hippocampus	Impairment of dorsoventral axis transmission
Alugubelly et al. (2021)	Chlorpyrifos	In vivo	Rat	Amygdala	↓ Glutamate AMPA receptor 2 ↓ Excitatory amino acid transporter 2 ↑ VGLUT2
López-Merino et al. (2022)	Chlorpyrifos	In vivo	Rat	Hippocampus	Impair mGluR-LTD Overactivation of MAPK/ERK pathway
GABAergic synapses					
Alugubelly et al. (2021)	Chlorpyrifos	In vivo	Rat	Amygdala	↑ GABA transporter 3 ↑ glutamate decarboxylase 2

Table 2 (continued)

Cholinergic synapses	OP	Type of study	Sample	Brain region	The main findings
Miscellaneous					
Speed et al. (2012)	Chlorpyrifos	In vivo	Mouse	Hippocampus	↓ synaptic transmission
Farizatto et al. (2019)	Paraoxon	In vitro	Rat	Hippocampus	↓ synaptic maintenance and plasticity
Zhong et al. (2021)	TPP	In vivo	Mouse	Hippocampus	Disturb synaptogenesis and neurotransmission
Hong et al. (2022)	TPP	In vivo	Mouse	Hippocampus	Disturb neural development and synaptic function

OP organophosphorus, *DFP* diisopropylfluorophosphate, *TPP* triphenyl phosphate, *Ach* acetylcholine, *5HT* serotonin, *AChE* acetylcholinesterase, *CAT* choline acetyltransferase, *AC* adenylyl cyclase, *CREB* cAMP response element-binding protein, *CHT* choline transporter, *DA* dopamine, *PKA* protein kinase A, *DARPP-32* dopamine- and cAMP-regulated phosphoprotein of M(r) 32 kDa, *GluR1* glutamate receptor 1, *Glut* glutamate, *VGLUT* vesicular glutamate transporter, *GSK-3β* glycogen synthase kinase-3 β, *Aβ* amyloid β, DOPAC 3,4 dihydroxyphenylacetic acid, *mGluR-LTD* metabotropic glutamate receptor-dependent long-term depression, *GSK-3β* glycogen synthase kinase-3β, Aβ amyloid β, AMPA receptor α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, *MAPK* mitogen-activated protein kinase.

[a]ACh projecting regions: frontal/parietal cortex, temporal/occipital cortex, hippocampus, striatum, midbrain, and brainstem

[b]5-HT projections regions: frontal/parietal cortex, temporal/occipital cortex, midbrain, and brainstem

Dopaminergic transmission

There are two in vivo studies that have reported that neonatal exposure of rats to parathion and chlorpyrifos could increase dopamine (DA) turnover and DA metabolites in the stratum, substantia nigra, and some of ACh and 5HT projecting regions of the brain in adulthood (Eells and Brown 2009; Slotkin et al. 2009c). Increased protein kinase A (PKA) dependent phosphorylation of dopamine- and cAMP-regulated phosphoprotein of M(r) 32 kD (DARPP-32) and increased release of DA due to AChE inhibition were also shown to happen in the striatum of mice and rats exposed to chlorpyrifos and paraoxon, respectively (Faro et al. 2018; Torres-Altoro et al. 2011).

Glutamatergic transmission

Three in vivo studies evaluated the effect of chlorpyrifos on neural transmission in different brain regions of mice and rats. The first study reported that chlorpyrifos could increase glutamate receptor 1 (GlutR1) subunit of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, PKA-dependent phosphorylation of GlutR1 in the striatum of mice (Torres-Altoro et al. 2011). Decreased glutamate AMPA receptor 2, decreased excitatory amino acid transporter 2, and increased vesicular glutamate transporter 2 (VGLUT2) were shown to be caused by chlorpyrifos in the amygdala of rats (Alugubelly et al. 2021). Impairment of metabotropic glutamate receptor-dependent long-term depression (mGluR-LTD), as well as overactivation of MAPK/ERK pathway in the hippocampus of rats under the effect of perinatal exposure to chlorpyrifos, were the finding of another in vivo study (López-Merino et al. 2022). An in vitro study conducted on basal forebrain neuronal cells indicated that exposure to chlorpyrifos could increase glutamate, glutaminase activity, VGLUT1, GSK-3β, Aβ, and phosphorylated tau proteins, which may be associated with the development of neurodegenerative diseases (Moyano et al. 2018). There was another in vitro study evaluating the effect of a nerve agent surrogate diisopropylfluorophosphate (DFP) on the dorsal and ventral hippocampal synaptic transmission and showed that DFP could impair glutamatergic transmission along with dorsoventral axis transmission via distinct cholinergic and noncholinergic mechanisms (Brown et al. 2020).

GABAergic transmission

Alugubelly and colleagues investigated the effect of postnatal exposure to chlorpyrifos on glutamatergic and GABAergic signaling in adolescence. They reported an imbalance between these pathways manifested by increased GABA transporter 3 and glutamate decarboxylase 2 in the amygdala of rats (Alugubelly et al. 2021).

Miscellaneous

Some experimental studies have evaluated synaptic functions in the hippocampus under the effect of OP compounds. Impairment of synaptic transmission, synaptic maintenance, synaptic plasticity, synaptogenesis, and neuronal development in the hippocampus of mice and rats have been reported to occur after exposure to OP compounds such as chlorpyrifos, paraoxon, and triphenyl phosphate (TPP) (Farizatto et al. 2019; Hong et al. 2022; Speed et al. 2012; Zhong et al. 2021).

Subcellular pathways involved in OP-induced neurotoxicity

The imbalanced state between the production of oxidants and the ability of the biological system to detoxify reactive products can lead to oxidative stress, which can damage the structure and function of macromolecules, along with mitochondrial dysfunction and inflammatory responses. Oxidative stress-related mechanisms are involved in developing some chronic disorders, among which neurodegenerative and neurodevelopmental disorders have been pointed out (Corona 2020; Singh et al. 2019; Usui et al. 2023). On the other hand, oxidative damage and inflammatory responses have been repeatedly reported to be involved in the toxic effects of OP compounds in short-term and long-term exposures. There have been well-documented studies indicating that the neurotoxicity of OP compounds manifested as neurological disorders is primarily mediated by increasing the production of reactive oxygen species (ROS), impairing cellular antioxidant defenses, mitochondrial dysfunction, neuroinflammation, autophagy, and apoptotic cell death. Table 3 summarizes some of the most important in vitro and in vivo experimental studies on the role of subcellular events in OP-induced neurological disturbances in different brain regions.

In vitro studies

Different in vitro model systems have been used for investigating the cellular and molecular mechanisms of OP-induced neurological disturbances. PC12 is a cell line derived from a rat adrenal medullary tumor (pheochromocytoma). It is one of the most widely used in vitro model systems in the field of neurotoxicology, with a particular concentration on neural differentiation. The results of four studies conducted on PC12 cells indicate that exposure to chlorpyrifos and dichlorvos can cause an increase in ROS generation and oxidative stress markers, as well as decrease neurite outgrowth. Decreased activity of mitochondrial complex I and increased release of mitochondrial cytochrome c into cytoplasm have also been shown to occur in PC12 cells after exposure to these two OP pesticides implicating mitochondrial dysfunction (Crumpton et al. 2000; Lee et al. 2012; Qiao et al. 2005; Wani et al. 2017). In addition to oxidative damage, dichlorvos glyphosate has been shown to activate caspase-3 and promote apoptotic and autophagic cell death in differentiated PC12 cells, implicating the role of OP compounds in the degeneration of dopaminergic neurons and the development of neurodegenerative disorders, particularly PD (Gui et al. 2012; Wani et al. 2017).

SH-SY5Y is a human neuroblastoma cell line that can be converted to functional neurons under the effect of specific compounds and is widely used as a model for studying neurodegenerative disorders. Two in vitro studies have investigated the molecular mechanism underlying apoptotic and autophagic cell death induced by chlorpyrifos in SH-SY5Y. Their results implicated increased ROS generation, oxidative stress markers, activation of mitogen-activated protein kinases (MAPKs), including p38, JNK, and ERK, induction of proinflammatory cytokines such as TNF-α and COX-2, nuclear translocation of NF-κB and apoptotic events (Lee et al. 2014b; Park et al. 2013).

The Neuro-2a cell line comes from mouse neuroblasts and is often used to research neuronal differentiation, axonal growth, and neurodegenerative pathways. Two in vitro studies have shown that exposure to two OP compounds, malathion, and chlorpyrifos, can lead to an increase in ROS generation, mitochondrial cytochrome c release, lysosomal membrane permeabilization, autophagy, activation of CHOP and caspase-3, and ultimately, apoptotic cell death (Lin et al. 2023; Venkatesan et al. 2017).

Singh and his colleagues conducted a study to investigate the impact of chlorpyrifos on dopaminergic cell death in two different in vitro models, which were N27 cells (immortalized murine mesencephalic dopaminergic cells) and LUHMES cells (human dopaminergic neuronal cells). The results showed that chlorpyrifos caused an increase in the production of ROS while decreasing mitochondrial transmembrane permeabilization (MTP), which ultimately led to autophagy and apoptotic cell death. The team also used a chromatin immunoprecipitation method to prove that the impairment of the transcription factor STAT1 was involved in triggering mitochondrial-dependent oxidative stress response and autophagy. These processes can ultimately lead to dopaminergic neurotoxicity and apoptosis (Singh et al. 2018). Another in vitro study conducted on mouse primary cortical neuronal cultures indicated that chlorpyrifos could increase the expression of genes involved in intrinsic apoptosis, particularly Bbc3, and when Bbc3 knockdown neuronal cultures were exposed to chlorpyrifos, endoplasmic reticulum (ER) stress responses, and protein clearance were elevated, so that high molecular weight α-synuclein and tau immunoreactive protein aggregates were significantly decreased in comparison with wild-type neuronal cultures (Anderson et al. 2021).

Research has explored the ways in which chlorpyrifos can be neurotoxic using cell lines derived from human stem cells. One study used human neural precursor cells (hNPCs) derived from human embryonic stem cells (hESCs) and found that chlorpyrifos increased the generation of ROS and the activation of NF-κB, leading to the release of mitochondrial cytochrome c (Lee et al. 2014a). Another study conducted on human induced pluripotent stem cells (iPSCs) indicated that chlorpyrifos can reduce cellular ATP levels and the expression of genes involved in neural differentiation, as well as the mitochondrial fusion protein mitofusin 1 (Mfn1). Knockdown of Mfn1 in iPSCs resulted in the

Table 3 Subcellular mechanisms involved in OP-induced neurological disturbances in different brain regions evidenced by experimental studies *in vitro* and *in vivo*

Study	OP	Type of study	Origin of sample	Brain region	The main findings
Crumpton et al. (2000)	Chlorpyrifos	In vitro	Rat	Adrenal medulla	↑ ROS ↓ neurite outgrowth
Qiao et al. (2005)	Chlorpyrifos	In vitro	Rat	Adrenal medulla	↑ oxidative stress markers ↓ neurite outgrowth
Lee et al. (2012)	Chlorpyrifos	In vitro In vivo	Rat	Adrenal medulla Substantia nigra	↑ ROS ↓ mitochondrial complex I activity ↑ apoptosis of dopaminergic neurons
Gui et al. (2012)	Glyphosate	In vitro	Rat	Adrenal medulla	↑ apoptotic events ↑ autophagy markers
Wani et al. (2017)	Dichlorvos	In vitro	Rats	Adrenal medulla	↑ oxidative stress markers ↑ mitochondrial cytochrome c release ↑ caspase-3 activation, apoptosis
Park et al. (2013)	Chlorpyrifos	In vitro	Human	Neuroblastoma (SH-SY5Y cells)	↑ ROS ↑ autophagic cell death
Lee et al. (2014a, b)	Chlorpyrifos	In vitro	Human	Neuroblastoma (SH-SY5Y cells)	↑ oxidative stress markers Activation of MAPKs (p38, JNK, ERK) ↑ proinflammatory cytokines (TNF-α, COX-2) ↑ nuclear translocation of NF-κB
Venkatesan et al. (2017)	Malathion	In vitro	Mice	Neuroblasts (Neuro-2a cells)	↑ mitochondrial cytochrome c release ↑ apoptotic events ↑ autophagy ↑ lysosomal membrane permeabilization
Lin et al. (2023)	Chlorpyrifos	In vitro	Mice	Neuroblasts (Neuro-2a cells)	↑ ROS generation ↑ CHOP activation ↑ caspase-3 activation and apoptotic events
Singh et al. (2018)	Chlorpyrifos	In vitro	Murine Human	Dopaminergic neurons (N27 cells) LUHMES cells	↑ ROS generation ↑ STAT1 activation ↓ MTP ↑ autophagy ↑ apoptotic cell death
Anderson et al. (2021)	Chlorpyrifos	In vitro	Mice	Cortical neurons (Primary cells)	↑ apoptotic events ↑ ER stress response ↑ autophagy markers
Lee et al. (2014a, b)	Chlorpyrifos	In vitro	Human	Embryonic stem cells	↑ ROS ↑ NF-κB activation ↑ mitochondrial cytochrome c release
Yamada et al. (2017)	Chlorpyrifos	In vitro	Human	Pluripotent stem cells	↓ ATP, ↓ Mfn1 ↑ mitochondrial fragmentation
Weis et al. (2021)	Chlorpyrifos	In vitro	Murine	Microglial cells (BV-2 cells)	↑ oxidative stress markers (NO, MDA, $\dot{O}_2$) ↑ microglial activation ↑ proinflammatory cytokines (IL-1β, NLRP3)
Slotkin et al. (2005)	Chlorpyrifos	In vivo	Neonatal rat	Whole brain	↑ oxidative stress markers ↓ neural differentiation
Slotkin et al. (2007)	Chlorpyrifos Diazinon	In vivo	Neonatal rat	Brainstem Forebrain	↑ oxidative stress markers

Table 3 (continued)

Study	OP	Type of study	Origin of sample	Brain region	The main findings
De Felice et al. (2016)	Chlorpyrifos	In vivo	Mice offspring	Cortex Hippocampus	↑ oxidative stress markers ↑ synthesis of F2-isoprostanes and PGE2 ↑ ASD-like traits
Cattani et al. (2017)	Glyphosate	In vivo	Neonatal rats	Hippocampus	↑ oxidative stress markers glutamate excitotoxicity depressive-like behavior
de Oliveira et al. (2022)	Glyphosate	In vivo	Rat offspring	Prefrontal cortex Hippocampus	↑ Oxidative stress markers ↑ ASD simulated symptoms
Gallegos et al. (2018)	Glyphosate	In vivo	Rat offspring	Hippocampus	↑ oxidative stress markers Changed cholinergic/glutamatergic pathways ↓ recognition memory
Gallegos et al. (2023)	Chlorpyrifos	In vivo	Mice	Whole brain	Changed redox balance Changed in cholinergic and glutamatergic enzymes' ↑ anxiogenic behavior ↓ recognition memory
Adedara et al. (2018)	Chlorpyrifos	In vivo	Rats	Mid-brain Cerebral cortex, Cerebellum	↑ activity of MPO, ↑ lipid peroxidation ↓ activity of AChE and antioxidant enzymes ↑ negative geotaxis Locomotor and motor deficits
Tian et al. (2015)	Chlorpyrifos	In vivo	Neonatal rats	Amygdala	↑ HMGB1 ↑ NF-κB, IL-6 and TNF-α
Zaja-Milatovic et al. (2009)	DFP	In vivo	Rat	Cerebrum Hippocampus	↑ ROS ↑ dendritic degeneration of pyramidal neurons
Binukumar et al. (2011)	Dichlorvos	In vivo	Rat	Substantia nigra Corpus striatum	↑ microglial activation ↑ proinflammatory cytokines (TNF-α, IL-1β, IL-6) ↑ NADPH oxidase
Arnal et al. (2019)	Dimethoate	In vivo	Rats	Cortex Substantia nigra	↑ lipid peroxidation ↑ mitochondrial cytochrome c release ↑ Bax/Bcl-2 ratio and caspase-3 activation
Astiz et al. (2013)	Dimethoate	In vivo	Mice	Striatum Hippocampus	↑ microglial activation ↑ proinflammatory cytokines (TNF-α, IL-6)
Sheikh and Sheikh (2020)	Chlorpyrifos	In vivo	Rats	Substantia nigra	↑ MDA and ↓SOD ↑ glial fibrillary acidic protein ↓ tyrosine hydroxylase
Mohammadzadeh et al. (2022)	Malathion	In vivo	Rats	Striatum	↑ apoptotic events ↑ α-synuclein
Karimani et al. (2021)	Diazinon	In vivo	Mice	Cerebral cortex Hippocampus	↑ oxidative stress markers ↑ neurodegeneration-related gene expression Altered mood and spatial learning Memory dysfunction
Hashem et al. (2022)	Diazinon	In vivo	Mice offspring	Cerebellar cortex	↑ swollen mitochondria ↑ hyperchromatic nuclei ↓ AChE level, ↑neurodegenerative changes
Lukaszewicz-Hussain (2008)	CFP	In vivo	Rat	Whole brain	↓ GSH ↑ antioxidant enzyme activity

Table 3 (continued)

Study	OP	Type of study	Origin of sample	Brain region	The main findings
Li et al. (2015)	DFP	In vivo	Rats	Hippocampus	↑ microglial activation ↑ proinflammatory cytokines (IL-1β, IL-6)
Abd El-Moneim Ibrahim et al. (2020)	Chlorpyrifos	In vivo	Rats	Whole brain	↑ lipid peroxidation ↓dopamine, serotonin, MAO-A and AChE

OP organophosphorus, *CFP* chlorfenvinphos, *DFP* diisopropyl fluorophosphate. *ROS* reactive oxygen species, *MAPK* mitogen-activated kinase, *TNF-α* tumor necrosis factor-α, *COX-2* cyclooxygenase-2, *NF-κB* nuclear factor-κ-light-chain-enhancer of activated B cells, *CHOP* C/EBP homologous protein, *STAT1* signal transducer and activator of transcription 1, *MTP* mitochondrial transmembrane potential, *ER* endoplasmic reticulum, *Mgn1* mitochondrial fusion protein mitofusin 1, *NO* nitric oxide, *MDA* malondialdehyde, *IL* interleukin, *NLRP3* NLR family pyrin domain containing 3, *PGE2* prostaglandin E2, *ASD* autism spectrum disorders, *MPO* myeloperoxidase, *AChE* acetylcholinesterase, *HMGB1* high mobility group box 1, *NADPH* nicotinamide adenine dinucleotide phosphate, *MAO-A* monoamine oxidase-A, *hNPCs* human neural precursor cells, *hESCs* human embryonic stem cells, *iPSCs* human induced pluripotent stem cells

downregulation of genes involved in neurogenesis, suggesting that the neurotoxic effects of chlorpyrifos were primarily mediated through the reduction of Mfn1 and mitochondrial fragmentation in iPSCs (Yamada et al. 2017).

Researchers conducted a study on BV-2 microglial cells from mice to examine the effects of exposure to chlorpyrifos, which can cause neuroinflammation. The results showed that the exposure caused an increase in microglial cell proliferation and activation, as well as a significant increase in the expression of oxidative stress markers like NO, MDA, and $\dot{O}2$, and proinflammatory cytokines such as IL-1β and NLRP3. This study was conducted by Weis et al. (2021).

In vivo studies

Different in vivo models have been applied to study neurodevelopmental and neurodegenerative toxicities of OP compounds in laboratory animals. Chlorpyrifos and glyphosate are two OP pesticides, most of which have been used in exploring the molecular mechanisms of OP-induced neurodevelopmental disorders. Slotkin and colleagues conducted two separate studies investigating the developmental neurotoxicity of chlorpyrifos in neonatal rats. It has been reported that being exposed to chlorpyrifos and diazinon in early infancy can result in a rise in oxidative stress markers in various brain regions, particularly the brainstem and forebrain. Furthermore, the use of chlorpyrifos has been found to alter the expression of genes that are responsible for the growth and differentiation of neurons, cell signaling, neurotransmitter synthesis, and storage, as well as synaptic neurotransmitter receptors (Slotkin et al. 2005; Slotkin and Seidler 2007).

In a mouse model of idiopathic autism, oxidative stress, manifested by increased synthesis of F2-isoprostanes and prostaglandin E2, has been shown to occur in the cortex and hippocampus of offspring exposed to chlorpyrifos during gestation (De Felice et al. 2016).

An invivo study has shown that glyphosate, a commonly used herbicide, can have adverse effects on neurodevelopment. The study found that exposure to glyphosate during pregnancy and after birth led to depressive-like behaviors in the offspring, as well as increased oxidative stress markers and changes in neurotransmission in the hippocampus. Another study also suggests that exposure to glyphosate during pregnancy and after birth can lead to oxidative stress in the hippocampus and prefrontal cortex of rat offspring, resulting in autism spectrum disorder-like symptoms such as impaired early social communication, olfactory discrimination, social play behavior, object exploration, and increased repetitive and stereotyped movements.

In separate studies, Gallegos and colleagues assessed the impact of glyphosate and chlorpyrifos on neurodevelopmental toxicity. They found that exposure to these pesticides can cause oxidative stress and affect the activity of neurotransmission enzymes in the hippocampus, leading to deficits in recognition memory and increased anxiety in exposed animals. Another study also showed that chlorpyrifos exposure in rats can increase myeloperoxidase and lipid peroxidation while decreasing the activity of antioxidant enzymes and AChE in the mid-brain, cerebral cortex, and cerebellum. Tian and colleagues administered chlorpyrifos to neonatal rats and found that it can trigger neuroinflammation in the amygdala, mediated by the HMGB1/TLR4/NF-κB pathway resulting in increased proinflammatory cytokines.

Some in vivo studies have evaluated subcellular mechanisms of OP-induced neurodegeneration in different brain regions of laboratory animals and mainly reported oxidative stress and neuroinflammation were involved. A study evaluating the effect of acute exposure to diisopropyl phosphor fluoridate (DFP) in rats reported an increase in the markers of oxidative stress and a decrease in high-energy phosphates in the cerebrum along with dendritic degeneration pyramidal neurons in the hippocampus (Zaja-Milatovic et al. 2009).

Some in vivo research explored the subcellular events in brain regions such as the corpus striatum and substantia nigra to find the pathological mechanisms of OP-induced PD. Nigrostriatal dopaminergic degeneration has been evaluated in an in vivo study that reported that chronic exposure to dichlorvos caused loss of dopaminergic neurons along with microglial activation and induction of NADPH oxidase as well as elevated expression of proinflammatory cytokines such as TNF-α, IL-1β and IL-6 in substantia nigra and corpus striatum of rats (Binukumar et al. 2011). Subchronic exposure to low doses of dimethoate has been shown to increase lipid peroxidation, release of mitochondrial cytochrome c, ratio of Bax/Bcl-2, and activation of caspase-3 in the substantia nigra and cortex of rats. Furthermore, the increase in pro-apoptotic events was correlated with a decrease in tyrosine hydroxylase-positive neurons in substantia nigra (Arnal et al. 2019). In addition, increased microglial activation and up-regulation of proinflammatory cytokines such as TNF-α and IL-6 have been found in the striatum and hippocampus of mice exposed to subchronic and low doses of dimethoate (Astiz et al. 2013). Subchronic exposure of rats to chlorpyrifos has also been shown to increase lipid peroxidation and glial fibrillary acidic proteins, decrease antioxidant enzymes, tyrosine hydroxylase, and proportion of neurons in substantia nigra (Sheikh and Sheikh 2020). Moreover, an in vivo study evaluating the effect of subchronic exposure to malathion in rats reported an increase in Bax/Bcl2 ratio, caspases 3 and 9 protein, mRNA, and protein level of α-synuclein in the striatum (Mohammadzadeh et al. 2022).

Subchronic neurotoxicity of diazinon was the aim of an in vivo study investigating mood, spatial learning, and memory function in mice. Diazinon was shown to increase oxidative stress markers and change the expression of genes involved in neurodegeneration, such as synaptophysin, vesicular acetylcholine transferase, and glutamate decarboxylase in the hippocampus and cerebral cortex. Altered mood manifested by increased anxiety and depressive-like behaviors, change in spatial learning, and memory dysfunction were also found to be caused by diazinon (Karimani et al. 2021). Prenatal and postnatal exposure to diazinon has also been shown to adversely influence the cerebellum development in the mice offspring, leading to neurodegenerative changes. The rough endoplasmic reticulum, swollen mitochondria, and shrunken hyperchromatic nuclei, as well as a decrease in the number of Purkinje cells, were found in the cerebellum of mice postnatally exposed to diazinon (Hashem 2022).

Some other studies are reporting increased markers of oxidative stress and neuroinflammation in different brain regions of rats exposed to different OP compounds such as chlorpyrifos, chlorfenvinphos (CFP), and DFP (Abd El-Moneim Ibrahim et al. 2020; Li et al. 2015; Lukaszewicz-Hussain 2008).

Genetic polymorphisms identified for OP-related neurodegenerative and neurodevelopmental disorders

Many studies have been carried out in epidemiological and experimental setups to find that genetic polymorphisms may affect susceptibility to the toxic effects of OP compounds. Polymorphism within a wide range of genes has been evaluated in association with the neurotoxicity of pesticides. The results of the main studies evaluating the role of genetic polymorphism in higher susceptibility to neurodegenerative and neurodevelopmental disorders are presented in Table 4.

Paraoxonase 1 (PON1) is a gene encoding a protein with arylesterase and paraoxonase activity, which can hydrolyze a wide variety of substrates such as lactones, thiolactones, aryl esters, OP oxons, and lipid peroxides. The PON1 gene is located on chromosome 7, and low PON1 activity due to genetic polymorphism has been reported to increase the susceptibility to the toxic effects of OP compounds. Since then, there have been great research efforts in identifying the role of PON1 genetic polymorphism in human susceptibility to OP neurotoxicity. On the other hand, PON1 genotypes have been much studied in association with human neurological and psychiatric disorders. Several single nucleotide polymorphisms (SNPs) in the PON1 gene have been identified to have a role in developing neurodegenerative and neurodevelopmental disorders (Marsillach et al. 2016; Reichert et al. 2020). L55R and Q192R are among the most widely studied variants of PON1. It has been reported that the link of OP exposure with the development of PD, ASD, cognitive dysfunction, neurological problems, and chronic intoxication was strengthened in the carriers of these SNPs (D'Amelio et al. 2005; Engel et al. 2011; Glass et al. 2018; Lee et al. 2013; Tawfik Khattab et al. 2016). PON1 genetic variants at 192 and -108T have also been reported to increase neurodevelopmental and neurobehavioral dysfunctions in children exposed to OP compounds (Eskenazi et al. 2010; Eskenazi et al. 2014). PON1 CT/TT (rs705381) has also been shown to modify the association of exposure to OP compounds with the incidence of ADHD in children (Chang et al. 2021).

ATP Binding Cassette Subfamily B Member 1 (ABCB1) is also an environment-susceptible gene coding the P-glycoprotein (P-gp) or multidrug resistance protein (MDR1). P-gp initially protects the body from the harmful effects of xenobiotics by pumping them out of the cells. ABCB1 gene is highly polymorphic, and its well-known SNPs may affect the expression and function of P-gp, leading to altered kinetic parameters of xenobiotics and overall outcomes of therapy or toxicity. Impaired function of P-gp has been reported to be associated with an increased risk of neurodegenerative disorders like PD (Ahmed et al. 2016). A population-based CC

Table 4 Epidemiological end-experimental studies evidence genetic polymorphisms involved in OP compounds' association with neurological disorders

Reference	Study type	Exposure assessment	OP compound	Disorder	Genetic variants
D'Amelio (2005)	CS	Indirect in vitro	Diazinon	ASD	PON1L55M, PON1Q192R
Hancock et al. (2008)	CC	Questionnaire	Pesticides	PD	NOS1 (rs12829185, rs1047735, and rs2682826)
Eskenazi (2010)	Co	Urine DAPs	OPs	Impaired neurobehavior	PON1 (-108T), PON1 (192QQ)
Engel (2011)	Co	Urine DAPs	OPs	Impaired cognitive development	PON1Q192R
Singh (2012)	CC	AChE activity	OPs	DNA damage	NAT2, GSTM1, GSTT1, CYP2C9
Lee (2013)	CC	GIS	Diazinon, Chlorpyrifos, Parathion	PD	PON1L55M, PON1Q192R, PON1C-108T
Eskenazi (2014)	Co	Blood DAPs	OPs	Impaired neurodevelopment	PON1 (-108T), PON1 (192QQ)
Narayan (2015)	CC	GIS	OPs	PD	ABCB1 (rs1045642), ABCB1 (rs2032582)
Paul (2016)	CC	GIS	OPs	PD	NOS1 (rs2682826), NOS2A (rs1060826)
Tawfik Khattab (2016)	CC	Poisoning	OPs	Chronic toxicity	PON1Q192R, CYP2D6 G1934A
Paul (2017)	Co	GIS	OPs	PD	PON1 L55M
Chang (2018)	CC	Urine DAPs	OPs	ADHD	DRD4 GG genotype
Glass (2018)	CS	Questionnaire	OPs	Neurotoxicity	NAT2 (rs1799931), PON1 192R (rs662), GSTM1
Paul (2018)	CC	GIS	OPs	PD	DNA methylation in ACh receptors pathways
Chang (2021)	CC	Urine DAPs	OPs	ADHD	PON1 (rs705381)
Wang (2021)	CC	Questionnaire	Omethoate	Reduced ChE activity	CYP2E1 (rs6413432)
Peris-Sampedro (2015)	In vivo	Mice exposure	Chlorpyrifos	AD	ApoE2, ApoE3, ApoE4
Peris-Sampedro (2016)	In vivo	Mice exposure	Chlorpyrifos	ADHD	ApoE2, ApoE3, ApoE4
Basaure (2019a)	In vivo	Mice exposure	Chlorpyrifos	Impaired social behavior	ApoE3, ApoE4
Basaure (2019b)	In vivo	Mice exposure	Chlorpyrifos	Impaired learning and memory	ApoE3, ApoE4
Biosca-Brull (2023)	In vivo	Mice exposure	Chlorpyrifos	Impaired social behavior	ApoE3, ApoE4
Modafferi (2021)	In vitro	iPSCs exposure	Chlorpyrifos	ASD	CHD8

Co cohort, *CC* case-control, *CS* cross-sectional, *DAP* dialkyl phosphate, *AChE* acetylcholinesterase, *GIS* geographic information system, *iPSC* induced pluripotent stem cells, *OP* organophosphorus, *ASD* autism spectrum disorder, *PD* Parkinson disease, *AD* Alzheimer disease, *ADHD* attention deficit hyperactivity disorder, *PON1* paraoxonase1, *GST* glutathione-s-transferase, *CYP* cytochrome P-450 oxidase, *NOS* nitric oxide synthase, *DRD4* dopamine receptor D4, *ApoE* Apolipoprotein E, *NAT2* N-acetyltransferase, *CHD8* chromodomain helicase DNA binding protein 8, *iPSCs* induced pluripotent stem cells, *ACh* acetylcholine, *ChE* cholinesterase

study has indicated that ABCB1 genotypes at two polymorphic sites, including rs1045642 (c.3435C/T) and rs2032582 (c.2677G/T/A), can increase the risk of PD in people occupationally exposed to OP pesticides (Narayan et al. 2015).

Nitric oxide synthase (NOS) is a family of enzymes responsible for producing nitric oxide (NO) from the amino acid L-arginine. NOS has three forms in mammals, including NOS1 (neuronal), NOS2 (inducible), and NOS3 (endothelial), with multiple functions in different parts of the body. The gene coding for NOS1 is located on chromosome 12 and is mainly involved in synaptic plasticity, smooth muscle relaxation, vasodilation, and blood pressure regulation. The gene coding for NOS2 is located on chromosome 17 and is activated in oxidative and inflammatory situations, implying the role of NOS2 in immunity. The NOS1 and NOS2 isoforms have been implicated in the pathogenesis of PD, ADHD, and ASD (Kavya et al. 2006; Kim et al. 2009; Weber et al. 2015). In a population-based CC study conducted on PD patients, the results indicated that exposure to OP compounds was more strongly associated with PD among participants carrying the genetic variant of NOS1 at rs2682826 and NOS2A at rs1060826 (Paul et al. 2016).

The dopamine receptor D4 (DRD4) gene is located near the telomere of chromosome 11p and encodes the D4 subtype of the dopamine receptor. This receptor is a G-protein coupled receptor acting by inhibition of adenylyl cyclase. DRD4 is a polymorphic gene primarily studied concerning psychiatric and neurodevelopmental disorders like ADHD and ASD (Amiri et al. 2022; Hasler et al. 2015; Ptácek et al. 2011). A CC study on children with ADHD reported that having the DRD4 GG genotype increases the dose-response relation between exposure to OP compounds and the risk of ADHD in children (Chang et al. 2018).

N-acetyltransferase 2 (NAT2) is a phase II metabolizing enzyme encoded by the NAT2 gene in humans and is responsible for the N-acetylation of xenobiotics such as aromatic amines and hydrazine derivatives. Sporadic reports implicate the role of NAT2 polymorphism in some neurodegenerative disorders like PD (Pandi et al. 2020). Some gene-environment studies have indicated that DNA variants of NAT2 can modify neurotoxicity and DNA damage in people occupationally exposed to OP compounds (Glass et al. 2018; Singh et al. 2012).

Glutathione S-transferase (GST) is a family of phase II metabolizing enzymes detoxing xenobiotics and oxidative stress products by conjugating reduced glutathione to electrophilic substrates. Because of polymorphic alleles encoding GST isozymes, there can be differences in the expression and function of GST enzymes. In addition to susceptibility to toxic chemical substances, an increased risk of neurological and neurodegenerative disorders has been associated with GST genetic polymorphisms (Dasari et al. 2018; Piacentini et al. 2012). Gene-environment studies conducted on people exposed to OP compounds have reported that the association of OP exposure with neurotoxicity and DNA damage was intensified in carriers of GSTM1 and GSTT1 variants, respectively (Glass et al. 2018; Singh et al. 2012).

Cytochromes P450 (CYP) is a large family of metabolizing enzymes that oxidize many substrates like xenobiotics, fatty acids, and steroids. Polymorphisms of different CYP genes have become the main focus of a wide range of pharmacogenetic studies evaluating the diverse responses to drug therapies based on different variants of CYP genotypes. Nevertheless, the sole of some well-known CYP genetic variants, such as CYP2J2, CYP2E1, and CYP2D6, have been identified in the development of neurological diseases like AD and PD (Fan et al. 2022; Mellick 2006; Ur Rasheed et al. 2017; Yan et al. 2015). Three separate studies have examined the impact of polymorphic CYP variants on individuals exposed to OP compounds. The findings indicate that those who carry genetic polymorphisms for CYP2C9, CYP2D6, and CYP2E1 are more susceptible to OP-induced DNA damage, chronic toxicity, and decreased cholinesterase activity (Singh et al. 2012; Tawfik Khattab et al. 2016; Wang et al. 2021).

Apolipoprotein E (APOE) is a gene located on chromosome 19. It encodes the protein Apo-E, which is involved in the metabolism of fats and is the leading carrier of cholesterol in the brain. APOE is a polymorphic gene, and its three main alleles include APOE1, APOE2, and APOE3. The impact of the APOE genotypes in developing human chronic diseases like cardiovascular and neurodegenerative disorders has been indicated (Fernández-Calle et al. 2022). Some experimental studies on human APOE polymorphisms in targeted replacement mouse models evaluated the susceptibility of animals carrying the genetic variants of APOE to OP-induced neurodegenerative and neurodevelopmental disorders. Genetic variants of APOE2, APOE3, and APOE4 have been shown to increase the association of chlorpyrifos exposure with AD, ADHD, impaired social behavior, and impaired learning and memory in mice (Basaure et al. 2019a; Basaure et al. 2019b; Biosca-Brull et al. 2023; Peris-Sampedro et al. 2015; Peris-Sampedro et al. 2016).

Chromodomain helicase DNA binding protein 8 (CHD8) gene encodes a member of the chromodomain-helicase-DNA binding protein family involved in several processes, including transcriptional regulation, epigenetic remodeling, promotion of cell proliferation, and regulation of RNA synthesis. Whole-exome sequencing and subsequent targeted-sequencing studies have identified allelic variants of CHD8 in association with ASD (Wilkinson et al. 2015). A gene-environment interaction study conducted on human iPSC-derived 3D brain organoids (BrainSpheres) carrying an inactivating mutation in the CHD gene reported that exposure to chlorpyrifos synergistically reduced CHD protein level and increased some metabolic biomarkers of ASD, including elements of the cholinergic system, tryptophan, lactic acid, kynurenic acid, α-hydroxyglutaric acid, S-adenosylmethionine, and S-adenosylhomocysteine levels. Perturbed neurite outgrowth, imbalanced excitatory/inhibitory neurotransmitters, and lower dopamine levels were also observed in brain spheres carrying the CHD8 variant and exposed to chlorpyrifos (Modafferi et al. 2021).

Conclusion

OP compounds are still among the most widely used pesticides, and their residues in agricultural products have created much concern about their toxicity due to long-term exposures. Regarding their adverse effects on the central nervous system, many epidemiological and experimental studies have pointed to the association between OP compounds and

a higher incidence of neurodegenerative and neurodevelopmental disorders. In this work, the results of 64 epidemiological studies on the association of OP compounds with neurodegenerative and neurodevelopmental disorders have been systematically reviewed. In this way, the main findings of 62 experimental studies in vitro or in vivo on the pathological mechanisms involved in developing neurodegenerative and neurodevelopmental disorders by OP compounds have also been described. Although ChE inhibition and cholinergic overstimulation are the known mechanisms of OP toxicities, some intracellular pathways have been suspected of associating neurological diseases with exposure to OP compounds. Among these intracellular mechanisms, oxidative stress and related pathways have been paid attention to neurodegenerative and neurodevelopmental toxicities of OP compounds. Oxidative stress and related pathways have been shown to mediate some other toxic reactions, such as genetic and epigenetic damages attributed to pesticides and OP compounds (Mostafalou and Abdollahi 2012). However, the oxidant-antioxidant imbalance has been much studied in the pathophysiology of age-related human neurological diseases such as PD and AD (Abdollahi et al. 2014). Some genetic variations identified on the link of OP compounds with neurodegenerative and neurodevelopmental disorders are related to the polymorphism in the genes modulating oxidant and antioxidant homeostasis. PON1 is the most widely studied gene with variants in developing OP-induced neurotoxicity and neurological disorders. The product of this gene, the enzyme PON1, has been known to have antioxidant and anti-inflammatory properties and can protect against oxidative stress. NOS and GST are the other genes whose polymorphisms have been identified in the association of OP compounds with neurodegenerative and neurodevelopmental disorders. The product of these genes can also cope with oxidative situations in the cells and protect against the harmful effects of pro-oxidants. Some other genetic variants identified in the link of OP compounds with neurodegenerative and neurodevelopmental disorders are related to the genes involved in xenobiotic detoxification and biotransformation, such as ABCB1, NAT2, and CYP. The role of OP compounds in developing human neurological diseases, mainly neurodegenerative and neurodevelopmental disorders, has been supported by cogent evidence presented by epidemiological and experimental studies. Paying attention to the role of genetic polymorphisms in higher susceptibility to the development of neurological diseases on the one hand, and the close relation between dysfunction of the mentioned polymorphic genes and pathological mechanisms of OP compounds at intracellular (oxidative stress, inflammation, mitochondrial dysfunction, autophagy) and synaptic levels, it can be concluded that genetic variations are most probably involved in OP-induced neurodegenerative and neurodevelopmental disorders.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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