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REVIEW PAPER

Pesticides Exposure and Dopaminergic Neurodegeneration

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Abstract

Pesticides are widely used in the world for agriculture and industry. A lot of pesticide residues are observed in our air, soil, and water, which has been regarded as serious environmental contaminations. More and more researches begin to pay attention to the potential toxic effects of pesticides on human health. Till now, it has been confirmed that pesticides exposures are associated with carcinogenicity, neurotoxicity, pulmonotoxicity, reproductive toxicity, developmental toxicity, and metabolic toxicity. Pesticides exposure might play an important role in the pathogenesis of neurodegenerative diseases, such as Parkinson disease and Alzheimer disease. In this review, we focused on the relationship between the main commonly used pesticides and dopaminergic neurodegeneration. The main mechanism of neurotoxicity induced by pesticides exposure were also discussed. Additionally, it is known that the main histological hallmark of dopamine neurodegeneration is the presence of α-synuclein aggregates called Lewy bodies. Therefore, we also discussed the linkages between pesticide exposure and synuclein protein aggregation, which would be helpful to understand the etiology of neurodegeneration.

Keywords Pesticide · Neurotoxicity · Dopaminergic neurodegeneration · α-synuclein · Lewy body

Introduction

It is known that pesticide has been widely used in the world. It cannot be denied that pesticide has brought great benefits to mankind with its wide application from agricultural production to people's daily life (Mostafalou and Abdollahi 2017). However, pesticides have been recognized as the oldest and most used environmental contaminants in the world (Mostafalou and Abdollahi 2017; Rauh and Margolis 2016). In recent years, the potential toxicity of pesticides to humans have been widely concerned, especially to the central nervous system (Mostafalou and Abdollahi 2017). Meanwhile, the incidence of dopaminergic neurodegeneration, such as Parkinson's disease, is also very high in recent years (Heusinkveld et al. 2014). It has been widely recognized that several environmental factors have been involved in the etiology of dopaminergic neurodegeneration, especially pesticides. It has been proved that animals exposed to the pesticides, such as rotenone, dieldrin, heptachlor, maneb, paraquat, or their combination, leads to dopaminergic neurodegeneration(Burke et al. 2017; Costa 2015; Heusinkveld et al. 2014; Jones et al. 2014; Mohammadi et al. 2019; Naughton and Terry 2018). Accordingly, pesticide, as an environmental factor, its correlation with dopaminergic neurodegeneration has also been confirmed. Progressive loss of dopaminergic neurons in the substantia nigra with Lewy body is the most typical pathological feature of dopaminergic neurodegeneration. However, the exact cause of dopaminergic neurodegeneration is unknown. At present, dopaminergic neurodegeneration is believed to be a result of combination of genetic factors and environmental factors (Fleming 2017). A recent report about twin study for PD incidence suggested that genetic factors might not play a key role in the etiology of onset PD. It is indicated that the contribution of environmental contaminants might play a more important role in the cause of dopamine neurodegeneration of Parkinson's disease, especially pesticides (Burns et al. 2013; Jackson-Lewis et al. 2012; Jokanovic 2018). Thus, several PD-like models induced by pesticide, such as rotenone and paraquat, have also been established to help human understand the pathophysiology of PD in vitro and in vivo (Takahashi et al. 2009). Additionally, these models were also

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used to help human look for and evaluate therapeutic strategies to treat dopaminergic neurodegeneration. Therefore, in this review, we intend to discuss the role of major classes of pesticides in their induced-dopamine neurodegeneration and a PD-like pathology. We hope this review will help us understand more about pesticides and dopaminergic neurodegeneration and the association of pesticides and PD.

Pesticides

It has been known that pesticides are a major group of chemicals used widely in commercial farming and home gardening in the world. Pesticides include an array of compounds designed to kill insects (insecticides), plants (herbicides), and fungi (fungicides), such as rotenone, paraquat, and maneb (Aloizou et al. 2020). It has been roughly estimated that there were at least about over five billion pounds of pesticides used in the world. More importantly, the number has grown rapidly in recent years. Therefore, more and more evidences show that pesticide residues can be easily found in the agricultural products and in the environment (Aloizou et al. 2020). And this phenomenon resulting in human exposure to these chemicals becomes an inevitable social problem. With the in-depth research, it has been found that humans can be contacted these pesticides through ingestion of pesticide residues in food and drinking water (Burns et al. 2013; Mostafalou and Abdollahi 2017). And moreover, occupational exposure to pesticide is more significantly especial to agricultural field workers and workers in the pesticide industry (Burns et al. 2013). It has been found that pesticide often shared the same molecular targets between target pest and non-target species, including humans. In 1962, Rachel Carson's book *Silent Spring* firstly raised public awareness about pesticides and their toxic effects in our environment. Therefore, more and more research has confirmed that pesticides can disrupt the function of different organs in the human body, affecting the nervous system, endocrine systems, reproductive system, and so on. Till now, the most prominent manifestation is the neurotoxicity of pesticide, affecting mammalian brain. Sara Mostafalou have reported that neurotoxicity has been ordered as the second-ranked toxicity of pesticides in their review, only second to tumor (Mostafalou and Abdollahi 2013). It is known that the major kinds of pesticides, such as organochlorines, organophosphoruses, and carbamates, mainly target some components of the nervous system (Costa 2015; Mostafalou and Abdollahi 2018). Therefore, their neurotoxicity for human is inevitable.

In fact, the role of pesticides in neurodegenerative diseases has long been suspected (Ayton et al. 2019). And published studies reported exposure to pesticides, such as paraquat, maneb, rotenone, and dieldrin, are not only linked to their acute effects but also contribute to chronic neurodegenerative disorders, most notably Parkinson's disease (Ayton et al. 2019). Therefore, more and more attention has been paid on the etiology of pesticide-induced Parkinson's disease.

The hypothesis that exposure to pesticides can significantly increase Parkinson's disease risk was indicated firstly by the discovery of MPTP (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine). It is known that MPTP is a classical proparkinsonian molecule. When entering the body, it can be converted into MPP+ (1-methyl-4-phenylpyridinium ion, an active metabolite of MPTP in vivo). MPP+ has been confirmed to be neurotoxic in the body. (Bhurtel et al. 2019). MPP+ can induce some symptoms which is very similar to PD in rats exposed to MPTP. At present, MPTP has been considered as a classical inducer for the establishment of PD model. In the process of studying the relationship between pesticides and neurotoxicity, it was found that the chemical structure of paraquat was similar to MPP+ . It is known that paraquat is one kind of important pesticides. Therefore, since then, attention has been paid to the relationship between paraquat and PD. Subsequently, more and more scholars have found that the pathogenesis of neurodegenerative diseases is closely associated with farming as an occupation, rural living, and well-water exposure. Now it has been widely accepted that pesticides indeed can cause neurotoxicity pathology in both animal models and humans.

The first well-known study about the association of pesticide and PD originated from the evaluation of PD prevalence in a homogeneous population in Quebec, Canada in 1986, which was found high rates of prevalence in areas of pesticide use. In France, it also has been reported that there is a positive association between pesticide exposure and PD risk. In the CPS-IIN cohort, it was reported that the participants exposure to pesticides was associated with a doubling of Parkinson's disease risk. In the Agricultural Health Study (a large American cohort study of over fifty thousand pesticide applicators and their spouses), positive associations were found between disease risk and exposure to pesticides, especially those pesticides known to affect mitochondrial complex I (including rotenone) or to cause oxidative stress (including paraquat). To some extent, PD has been considered as a professional disease for farmers professionally exposed to pesticides. Overall, the evidence that pesticide exposure increases Parkinson's disease risk is substantial. However, even with some limitations, many studies have found an association on the onset of PD with specific pesticides, which will be summarized, respectively, in the following.

Rotenone

Rotenone is a commonly used natural organic insecticide extracted from the roots of several plant species to kill fish in

reservoirs. It is a natural compound insecticide with hydrophobic and lipophilic properties. And it was once considered as a "safe and reliable" pesticide. However, human epidemiological studies showed that people often exposed to rotenone are more likely to develop dopaminergic neurodegeneration, such as PD. Among the most well-known studies are those performed in the large AHS cohort. In addition, the Farming and Movement Evaluation study (FAME), a small nested study within the AHS with only 69 cases and 237 controls, also determined that rotenone exposure was associated with PD regardless of the use of protective gloves. However, the relationship between rotenone and dopaminergic neurodegeneration has been controversial for a long time, until Greenamyre group reported that rotenone administered systemically to rats can induce the hallmarks of PD for the first time. From then, the rotenone-induced PD-like model gained widely attention.

With highly lipophilic, rotenone can easily cross the blood–brain barrier, pass through the biofilm, enter the central system, and combine with dopamine neurons. Therefore, rotenone entering into dopamine neurons does not depend on the dopamine transporter, which is a transmembrane protein and locates in dopamine neurons. When rotenone enters into the cell, it accumulates at mitochondrial complex I and then inhibits the transfer of electrons from iron–sulfur (Fe–S) centers to ubiquinone, leading to ROS formation and producing oxidative damage to DNA and proteins of neural cells. It is also believed that rotenone can directly induce dopamine neuron to release excessive dopamine, resulting in an imbalance of dopamine metabolism to induce cascade reaction of dopamine self-oxidation forming a large number of ROS, which damaged to the dopamine neurons. Additionally, rotenone can also decrease the mitochondrial membrane potential and increase voltage-dependent anion channel (VDAC), caspase-3, and caspase-9 protein levels, indicating an association of dopamine neurons apoptosis with rotenone. In recent years, it was reported that rotenone can affect the morphology and function of mitochondria and destroy the mitochondrial dynamics, leading to the imbalance of the mitochondrial homeostasis and neuron death. More reports show that rotenone can inhibit proteosome activity, which would fail to catalyze the degradation of ubiquitin-tagged proteins implicating in the pathogenesis of both genetic and sporadic forms of PD. It also has been confirmed that when rotenone enters into the body, it can promote the sensitivity of dopamine neurons to other toxic substances.

Rotenone is widely used as a model-inducing drug of Parkinson's disease. In rat models with administration of rotenone by daily intraperitoneal injection, it could produce bradykinesia, postural instability, and rigidity responsive to dopamine. It was found that nearly half of substantia nigra and striatal neurons were lost in postmortem rat studies treated with rotenone. Compared with the classic inducing drugs, its advantage is that it can replicate Lewy bodies formation in neuron (Johnson and Bobrovskaya 2015). It was found that alpha-synuclein and polyubiquitin-positive aggregates were observed in dopamine neurons in the substantia nigra, similar to the Lewy Bodies found in PD (Johnson and Bobrovskaya 2015). It has been reported that rotenone induces α-synuclein aggregation and finally causes dopamine neuron degeneration in PD models. As for the mechanism of α-synuclein aggregation induced by rotenone is unknown, but it has been demonstrated that rotenone can increase intracellular calcium and stimulate phosphorylation and aggregation of α-synuclein. In addition, it has been known that autophagy normally can help degrade aggregated α-synuclein to prevent α-synuclein accumulation in neuron cells. However, rotenone also has been found to impair autophagy, which would stimulate the formation of aggregated α-synuclein. Apart from directly inducing α-synuclein accumulation, rotenone can induce the dysfunction of the proteasomal system and further lead to aggregated α-synuclein. Of course, there are other signaling pathways mediating α-synuclein aggregation following rotenone exposure. In addition, rotenone can also lead to phosphorylation and aggregation of tau and amyloid proteins. Therefore, the major advantage of the rodent rotenone model is its ability to induce the formation of α-synuclein-positive cytoplasmic inclusions in dopamine neurons, which can replicate the neuropathological hallmark of Lewy bodies seen in PD.

Paraquat

Paraquat is a kind of herbicide and is widely used in farm in developing countries. Its structure is similar to neurotoxin MPT+ (Chia et al. 2020; Smeyne et al. 2016). Therefore, paraquat also has neurotoxicity similar to MPTP effect (Smeyne et al. 2016). Since then, there has been great interest in paraquat due to its chemical structure closely resembling the active metabolite of MPTP. Paraquat has been considered to be a stronger environmental factors in the occurrence of Parkinson's disease (Bastias-Candia et al. 2019). And it also has been used to establish animal models to simulate the aspects of PD pathology, such as dopamine neuron loss and synuclein aggregation (Bastias-Candia et al. 2019; Cook et al. 2016; Nistico et al. 2011).

It has been suggested that paraquat can directly penetrate the blood–brain barrier with a slow speed and small amount (Thompson and Zhang 2016). Paraquat is suspected to enter the brain by neutral amino acid transporters and is subsequently into the cells in a sodium-dependent fashion, and accumulates in the mitochondria. Once within the cells of the brain, paraquat acts as a redox cycling compound at the cytosolic level, leading to too much oxygen-free radical generation and promoting

the oxidative stress reaction. In addition to increasing oxidative stress, paraquat exposure also can increase the release of IL-6 to promote neuroinflammation to initiate processes associated with dopamine neurodegeneration (Stojkovska et al. 2015). It also can result in the inhibition of the mitochondrial respiratory chain complex I activity and the synthesis of adenosine triphosphate (Huang et al. 2016). In recent years, it has shown that paraquat can activate Bak protein, a pro-apoptosis Bcl-2 family member to induce apoptosis (Huang et al. 2014). In addition to these classic mechanisms of action, recent reports have demonstrated that paraquat can induce conformational changes of α-synuclein and promote α-synuclein aggregation to stimulate microglial activation (Navarro-Yepes et al. 2016). Paraquat also can suppress proteasomal degradation activity to promote α-synuclein overexpression (Fleming 2017; Naudet et al. 2017).

Recently, in SH-SY5Y cells, paraquat was found it could promote tyrosine phosphorylation of parkin, which led to the inhibition of the protein's function and accelerated PD progression (Sun et al. 2018). Additionally, exposure to paraquat also can boost hyperacetylation in vitro models of Parkinson's disease (Wills et al. 2012). Therefore, the mechanism of epigenetic reprograming may also play an important role in paraquat-induced Parkinson's disease. Taken together, based on these different mechanisms, paraquat eventually can induce dopamine neuron degeneration and death.

Recent studies have shown that systemic sub-chronic exposure to paraquat in mice can induce dopaminergic neuronal cell death, and however, total dopamine levels remain nearly unchanged. However, higher doses of chronic exposure did cause slow progressive degeneration of dopamine neurons and delayed reduction of dopaminergic neurotransmission (Wang et al. 2018). Also it was reported that there were susceptibility alleles in dopamine transporter of dopamine neuron. Except for paraquat being transported by dopamine transporter, PQ(+) (the metabolite of paraquat) is also a substrate for the organic cation transporter 3 (Oct3, Slc22a3) with abundant expression in non-dopamine cells in the nigrostriatal regions. Therefore, when exposed to paraquat, nigrostriatal damage can be modulated by dopamine transporter and Oct3 induced by PQ(2+)/PQ(+) redox cycling (Rappold et al. 2011). Moreover, exposure to maneb and paraquat concurrently led to higher PD risk (Richter et al. 2017; Ritz et al. 2009). These results suggest that paraquat may often cause a "subclinical" insult, and additional environmental or genetic factors may further be required for PD to develop (Colle et al. 2018). Of course, it is also an example of synergistic effects of poisons, which needs to be focused in the future.

Maneb

The dithiocarbamate fungicide maneb was first registered as a broad-spectrum pesticide in the United States in 1962. Maneb is a low toxicity and protective fungicide and is also an irritant to respiratory tracts and is capable of inducing sensitization by skin contact. Maneb has attracted interest due to increasing concern of the negative health effects of pesticides, as well as its association with Parkinson's disease.

Maneb has been studied little individually. Therefore, knowledge of the mechanisms of this toxin is very limited. The current evidences suggest that maneb seems to cross the blood–brain barrier directly and preferentially inhibits mitochondrial complex III. As for the association of maneb with PD, there are some disputes. In one early study, it has been reported that it is associated with Parkinsonism in humans. However, some studies have shown that single chronic exposure of maneb in vivo has no obvious effect in the motor behavior, dopamine level, and histopathology in the substantia nigra of the brain in mice. Therefore, part researchers thought that single exposure of maneb does not easily lead to neurotoxicity in mice. However, epidemiologists have found some interesting data that paraquat and maneb were often used in the same geographical regions, with increased incidence of PD disease (Thrash et al. 2007). Additionally, several human case–control studies and laboratory studies also support an association between maneb, paraquat, and PD. Therefore, it is believed that when the combination of paraquat and maneb is exposed, paraquat and maneb will have a certain synergistic effect to induce neurotoxicity (Hou et al. 2017). In vivo experiments showed paraquat and maneb combined exposure can cause denaturation of dopamine neurons and induce some SD rats to show weight loss, tremor, and respiratory distress. In vitro experiments, it was shown that the microglial cells exposed to paraquat and maneb led to the loss of locus coeruleus neurons, which is one of the common characteristics of some neurodegenerative disease. Additionally, direct action of paraquat and maneb on microglia cells can lead to protein processing dysfunction in dopamine neurons of substantia nigra. Therefore, as so far, paraquat and maneb combined exposure has been used to model aspects of Parkinson-like motor deficits in rodents and to investigate the mechanisms of Parkinson's disease.

Pyrethroids

Pyrethroids are derived from the structure of natural pyrethroids and are a newer class of synthetic insecticides often contained in household insecticides and mosquito repellants. Pyrethroid insecticide is a kind of broad-spectrum insecticide with high efficiency and low toxicity.

The main neurotoxic mechanisms of pyrethroid insecticide include oxidative stress, inflammation, and mitochondrial dysfunction (Mohammadi et al. 2019). And more, voltage-gated sodium channels are also their main neurotoxicity targets in the body (Rameshgar et al. 2019; Silva and Scott 2020). Mainly because they can prolong the opening time of sodium ion channels on the surface of nerve cells, then further to cause the depolarization of cell membrane, finally leading to nerve cell damage (Costa 2015; Rameshgar et al. 2019). The secondary targets of pyrethroid neurotoxicity are calcium and chloride channels (Clark and Symington 2012; Soderlund 2012). Other receptors, enzymes, and several signaling pathways also can participate in the disorders induced by pyrethroids (Soderlund 2012). In recent years, there have been more and more studies on the effects of pyrethroid pesticides on dopamine nervous system in the substantia nigra, of which deltamethrin and cypermethrin are the most representative.

Many reports have indicated that deltamethrin is associated with the risk of neurotoxicity (Baskar and Murthy 2018; Christen et al. 2017). Exposure to deltamethrin can lead to a reduction of dopamine content and dopamine transporter in the striatum of rats. Deltamethrin also can inhibit the expression of tyrosine hydroxylase, reducing the synthesis of endogenous dopamine. (Kung et al. 2015; Souza et al. 2018). All of the results mentioned above suggest that there might be an association between deltamethrin and PD. The toxicity of deltamethrin in the brain has also been demonstrated that it can inhibit acetylcholinesterase activity, probably due to its lipophilic nature (Singh et al. 2018). Additionally, it cannot only alter voltage-sensitive sodium channel kinetics but also can target ligand-gated ion channels (GABA receptors, nicotinic acetylcholine receptors, and glutamate receptors) to inhibit the nerve impulse (Singh et al. 2018; Taylor-Wells et al. 2015). As for cypermethrin, it can across the blood–brain barrier directly. Cypermethrin exposure can lead to a promotion of oxidative stress, a reduction of vesicle monoamine transporter expression, and a decrease of dopamine content, finally causing the death of dopamine neuron in the substantia nigra (Abd et al. 2020; Mezni et al. 2020; Mohammadi et al. 2019; Romero et al. 2017). Therefore, the results suggested that pyrethroids might increase the risk of PD by interfering with the function of the substantia striatum system. However, this area requires further study, as there is little specific human data besides the general finding that pesticide exposure, including pyrethroids, is associated with PD.

Organochlorine pesticides

Organochlorine pesticides are a kind of compounds containing organochlorine elements used to control plant diseases and insect pests extensively. They have high lipid solubility and can penetrate various cell membranes. Their properties are stable and are not volatile. Thus, they can easily persist in the environment and accumulate in the organisms, such as fruits, vegetables, grains, dairy products, and meats, leading to human exposure to organochlorine pesticides (Richardson et al. 2019). In a case–control study, it is reported that professional organochlorine exposure was associated with increased PD risk. Of note, it is also found a higher concentration of organochlorine compounds in PD brains, specifically in the striatum, compared with the brains of patients without PD (Saeedi and Dehpour 2016). Therefore, these chemicals have been banned in the United States since they were suspected to be neurotoxicity and have been associated with PD.

However, the correlation between organochlorine pesticides and PD is controversial. In a prospective investigation in Finland, blood concentrations of organochlorine pesticides were not directly associated with Parkinson's disease risk (Weisskopf et al. 2010). These results suggest that the association of organochlorine pesticides and PD may require further verification.

Organochlorine pesticides are divided into two categories: benzene as raw material and cyclopentadiene as raw material, respectively. Organochlorine pesticides with cyclopentadiene as the raw material are reported to have correlation with neurodegenerative diseases, among which dieldrin is the most representative (Baltazar et al. 2014; Cao et al. 2018). Dieldrin is a highly toxic organochlorine pesticide which has been abandoned use in the 1970s in many developed countries. However, dieldrin is a kind of compounds with high stability and lipophilicity, and it has been found to persist in the environment. Humans can be exposed to dieldrin through contaminated ground water, food, and residuals in the environment. Dieldrin can be easily absorbed through the skin, stored in fatty tissues for extended periods of time. Dieldrin can penetrate into the blood–brain barrier, and has been classified as a persistent organic pollutant. It also has been found an elevated levels of dieldrin in the serum of humans exposed to dieldrin (Chhillar et al. 2013).

Previous epidemiology studies have shown a positive association between dieldrin exposure and PD risk (Baltazar et al. 2014; Chhillar et al. 2013). In a case–control study in the North Indian population, it was found that dieldrin was the most frequently detected organochlorine pesticide through analyzing serum samples for five organochlorine pesticides (Chhillar et al. 2013). The result mentioned above was present in 9.3% of control and 61.4% of PD respectively. Additionally, it has been detected that high dieldrin levels appeared in the brain autopsy of PD patients compared to age-matched human control brains (Chhillar et al. 2013). Therefore, all these results indicated that increased level of dieldrin may be associated with the higher risk of PD. In vitro studies, dieldrin shows

selectively neurotoxic to dopaminergic neurons, with comparatively lower toxicity to GABAergic neurons.

Neuronal ion channels have been shown to be targets of dieldrin in neuron cells. Except for that, the mechanisms of dieldrin-induced dopaminergic cell death currently focused in dopamine release, apoptosis, and oxidative stress. It has been shown dieldrin can induce alteration of the dopamine uptake and neurotransmitter release in vivo. (Bloomquist et al. 2002). Additionally, releases of dopamine and its metabolite were promoted to accelerate the depletion of intracellular dopamine in PC12 cells exposed to dieldrin (Kitazawa et al. 2001). Dieldrin exposure in PC12 cells induces chromatin condensation in the nucleus (Kitazawa et al. 2003). Dieldrin can induce apoptosis via both caspase-independent and caspase-dependent reactive pathway in SN4741 nigral dopaminergic cell line (Chun et al. 2001).

It is also believed that mitochondrial redox signaling might be an upstream event of dieldrin-induced dopaminergic neurotoxicity (Song et al. 2019). Dieldrin exposure also could induce mitochondrial dysfunction and ubiquitin–proteasomal dysfunction (Rhodes et al. 2013; Schmidt et al. 2017). Nr4a2, Lmx1b and GSTP1 genes may be considered as candidate genes for PD. Disruption the expression of these genes were also associated with dieldrin exposure in vivo, with obvious neurochemical changes (Kochmanski et al. 2019; Singh et al. 2014). Recently, it was also reported that epigenetic dysregulation through hyperacetylation of core histones was also observed in cell and mouse models exposed to dieldrin (Kochmanski et al. 2019). More importantly, it was found that dieldrin can stimulate conformational change as well as fibrillization of α-synuclein (Hatcher et al. 2007). Sun and colleagues also reported that dieldrin exposure can promote α-synuclein expression and disrupt the ubiquitin proteasomal system, which leads to dopaminergic neuronal cells more susceptible to apoptotic cell death (Sun et al. 2005). Therefore, these potential molecular mechanisms identified so far might contribute to increased PD risk exposed to dieldrin. However, even though dieldrin can induce ROS generation, mitochondrial dysfunction, oxidative stress, α-synuclein aggregation, and dopamine depletion, it still fails to stimulate motor deficits commonly seen in PD patients. Under normal conditions, compared with rotenone, relatively high concentrations of dieldrin exposure are needed to produce the above damages. Therefore, the effects of dieldrin on neuron are weak compared with rotenone which requires relatively low concentrations to cause similar effects. However, an in vitro study did find that dieldrin with even at low, nanomolar concentrations disrupted calcium homeostasis of dopaminergic cells, suggesting that further in vivo study should be performed (Heusinkveld and Westerink 2012).

Organophosphate pesticides

Organophosphates compounds appeared in the world in the late 1930s and are the most widely used pesticides in the agriculture due to their effectiveness. There are more than 100 organophosphates compounds in use around the world. However, as a consequence of their wide spread use as pesticides in the world, it has been reported that organophosphates (and their residues) are one kind of the most common synthetic chemicals detected in the environment, as well as in plant, animal, and human tissues in the worldwide. The deleterious effects of organophosphates on human health have also been concerned for decades. The National Health and Nutrition Examination Survey (NHANES) found that measurable levels of organophosphates pesticide metabolites were detected in their urine in more than 50% of the participants of NHANES 2011 from 1999 to 2000 in American (Min et al. 2011). Today, restrictions on the use of organophosphorus pesticides have been strengthened in the worldwide to reduce the toxic exposure to humans. However, in some countries, chronic and acute exposure remains as a persistent problem that needs to be concerned.

Organophosphates are pesticides that have known acute neurotoxic effects. Decreased activity of dopamine transporter uptake of dopamine were observed in mice intraperitoneally injected with thiophosphorus chloride (one kind of organophosphates). It was reported that acute organophosphates pesticide poisoning can present reversible PD-like symptoms. However, it cannot induce PD-related typical PD symptoms and pathological changes in animal models, which is very puzzling. It is known that the dopamine system and the cholinergic system are antagonistic to each other in the extrapyramidal system. Acetylcholinesterase activity can be inhibited by organophosphorus pesticides, which result in the two systems being out of balance, and corresponding extrapyramidal symptoms occurring. Therefore, PD-like symptoms caused by organophosphates pesticide may be attributed to the break of the balance between the two systems. That is why PD-like symptoms induced by organophosphorus pesticides is reversible.

However, it has been accepted that organophosphates exposure was linked to the risk of Alzheimer's disease with many epidemiological and laboratory evidences (Chen et al. 2012). There is a lot of evidence to show that higher rates of ambient organophosphate exposure were also associated with higher PD risk (Hernandez et al. 2016). It has been reported that chlorpyrifos is one of the most potent organophosphates and is associated dopaminergic cell death. Moreover, it was observed that the alterations in the locomotor activity do not correlate well with the degree of AChE inhibition in brain of mice and rats exposed to chlorpyrifos. It was suggested that the neurotoxicity induced by chlorpyrifos might attributed to mitochondria-mediated oxidative

stress response. In vivo study showed chronic and low level of organophosphates exposure can lead to the abnormalities of sensorimotor gating, spatial learning, recognition memory, cognitive flexibility and sustained attention, and so on. In vitro study showed long-term dopaminergic cell loss and microglial activation could been observed in neonatal animals exposed to the chlorpyrifos, one kind of organophosphorus pesticides (Lee et al. 2014).

It has been confirmed that paraoxonase-1 (PON1) can detoxify organophosphorus pesticides and the common genetic variant of an enzyme was important in detoxifying organophosphates. It was found that this genetic variant of the enzyme contributed to a greater than two-fold increased risk in PD (Lee et al. 2013; Paul et al. 2017). It was known that many organophosphorus pesticides can be bioactivated into a toxic oxon form with entering the bloodstream. When the oxon form escaping liver detoxification, serum paraoxonase (PON1) can further hydrolyze the oxon in the blood before it reaches the brain(Paul et al. 2017). Therefore, the variable vulnerability to organophosphate neurotoxic effects can be mainly attributed to the common genetic variant of PON1 activity between individuals (Lee et al. 2013; Paul et al. 2017). That is partially to explain the different conclusion about the association of organophosphates and PD.

Atrazine

Atrazine is a low toxicity and long duration of triazine herbicide. It was widely used in the world. In recent years, more and more concern has been focused in the fact that atrazine is more often detected in ground and surface waters. It has also been suggested that PD prevalence are associated with the increasing levels of atrazine in groundwater.

In recent years, it was reported that dopaminergic neuron was affected with atrazine exposure with large number of evidences (Figueira et al. 2017; Rodriguez et al. 2013; Walters et al. 2015; Zhang et al. 2015). Till now, the neurotoxic effects of atrazine exposure on dopamine neurons have been reported with many different mechanisms. The most important mechanism is mainly focused on disrupting dopamine pathways, including dopamine synthesis, metabolism, and transport. For example, protein expression of Nurr1, DAT, VMAT2, and TH were also reduced in SD rats exposed to atrazine. Therefore, the reduction of dopamine levels was mainly attributed to the interference with the vesicular storage and/or cellular uptake of dopamine exposure to atrazine (Hossain and Filipov 2008). Additionally, neurochemistry alteration was also observed in the substantia nigra of animal models exposed to atrazine (Rodriguez et al. 2017). Moreover, atrazine and its metabolites could directly affect the uptake of dopamine neurons, which resulted in an increase of the level of free dopamine in cytoplasm and promoted the production of oxidative stress. Finally, cell apoptosis appeared in the dopamine neurons (Hossain and Filipov 2008; Li et al. 2014). Additionally, the number of dopamine neurons was also decreased in mice treated with atrazine (Lin et al. 2013). It was also reported that rats exposed to atrazine led to a reduction of L-dopamine. Moreover, genes expression of NuIP, Nurr1, and p57kip2 were reduced in the nigra–striatum of animals exposed to atrazine (Li et al. 2015; Sun et al. 2014; Walters et al. 2015).

It has also been found that miRNA-7 was participated in regulating the BDNF/α-synuclein axis with atrazine-induced PD rats model (Li et al. 2019a, b). Moreover, it was reported that the MEK/ERK/CREB signaling pathway was involved in inducing functional and morphological damage in the neurons exposed to atrazine (Li et al. 2019a, b; Li et al. 2018). Additionally, atrazine could induce microglia activation to reduce SH-SY5Y cell activity, leading to SH-SY5Y cell apoptosis in in vitro experiments (Ma et al. 2015; Zhang et al. 2015). In addition, LC3-II mediating mitophagy through SOSTM1/p62 pathway was also participated in atrazine induced- dopaminergic neurons toxicity (Ma et al. 2018). While the study about atrazine on the signal is few, which reminds us that we might pay more attention to further explore.

Simazine

Simazine is a heterobenzene herbicide. Simazine was widely used in agricultural and non-agricultural fields since the 1960s, with high potency and a broad spectrum of killing weeds. However, just owing to its overuse in the world, simazine can be detected widely in soil and ground water samples in recent years. (Sousa et al. 2016). Especially, it has been found there are high levels of simazine in water, which are harmful to wildlife particularly aquatic organisms (Sai et al. 2016). In recent years, environmental exposure to human health has been focused. It was reported that simazine could be absorbed into the body through water and air. It has been concluded that growing environmental exposure of simazine increases the risk to human health, especially neurotoxicity in mammalian dopamine neurons.

Studies have shown that dopamine neurons are sensitive to simazine. For example, it was found that when MN9D cells exposed to simazine, cell morphology was destroyed and cell differentiation and growth were inhibited, which resulted in a decrease of cell viability (Li et al. 2017). In addition, it was found that simazine can inhibit the activity of tyrosine hydroxylase in MN9D cells. It is known that tyrosine hydroxylase is associated with the metabolism of dopamine. (Yu et al. 2016). Additionally, it was found that simazine could decrease the levels of Nurr1, dopamine transporter and vesicular monoamine transporter 2, which would further influence on the transport of dopamine. Moreover, it was found that simazine could decrease the level of aromatic

1-amino acid decarboxylase and increase the levels of monoamine oxidase and catecholamine-O-methyltransferase, which impacted on the synthesis and metabolism of dopamine (Li et al. 2017). Therefore, simazine might influence the synthesis, transport and metabolism of dopamine and lead to a reduction of dopamine levels in the dopamine neurons, resulting the neurodegeneration of dopamine neuron and eventually contribute to neurological disorders of the dopaminergic system.

The pathological features of dopamine neurodegeneration related to pesticides

The main histological hallmark of dopamine neurodegeneration is the presence of fibrillar aggregates called Lewy bodies, a residual eosinophilic inclusion body of nerve cells, whose role in the pathological process of PD remains controversial (Kalia and Kalia 2015; Shahmoradian et al. 2019; Wakabayashi et al. 2007).

It has been found that neuronal loss is more easily found in the predilection sites for Lewy bodies in neurodegeneration. Therefore, the Lewy body formation has been considered to be a marker for neuronal degeneration. It has been found that alpha-synuclein is a presynaptic nerve terminal protein and a major component of Lewy body in various neurodegenerative diseases, suggesting that it may be closely related to the formation of Lewy body and the occurrence of Parkinson's disease (Wong and Krainc 2017). In the past years, it was commonly assumed that Lewy body caused neuronal cell death. However, recent studies have indicated that Lewy body may represent cytoprotective mechanism in dopaminergic neurodegeneration with the demonstration of α-synuclein as a component of Lewy body.

More and more studies have indicated that pesticides are important environmental factors in promoting α-synuclein aggregation leading to the onset of Lewy body in various neurodegenerative diseases, including PD. It has been reported that several known pesticides have a propensity to interact with α-synuclein gene, encoding for the protein α-synuclein prior to α-synuclein's misfolding into toxic moieties (Naughton et al. 2017; Xiong et al. 2016, 2012). In addition, pesticides entering into the body can directly destroy the structure of α-synuclein protein, affect the covalent binding of α-synuclein protein to ubiquitin, thus destroy the degradation pathway of protein ubiquitin, promote the aggregation of α-synuclein protein, and weaken the degradation of abnormal protein (Kumar et al. 2018). The reports of Uversky et al. also provide evidence of this interaction between α-synuclein and pesticides (Uversky et al. 2002). The co-culture of some specific insecticides and α-synuclein significantly increased the rate of a-synuclein fibrillation in vitro (Pifl et al. 2004). This suggests that pesticides may play a direct role in the formation of α-synuclein inclusion bodies in the pathogenesis of dopaminergic neurodegeneration. Pesticides have also been shown to elevate the levels of α-synuclein expression in neurons and promote α-synuclein aggregation in vitro and in vivo. In fact, in vitro experiments showed that pesticides, such as rotenone and paraquat, can interact with α-synuclein, thereby accelerating the fibrillation and aggregation (Naudet et al. 2017; Naughton et al. 2017).

Conclusions

Pesticides are a family of compounds widely used in the agricultural, industrial, and health areas, therefore resulting in continued human exposure inevitably. Regardless of acute poisonings, or chronic and sub-lethal exposure to pesticides, the association of pesticide with human health will be a concern in the world. Incidence of human diseases, especially neurodegeneration associated with pesticides exposure, has been an important research area. Till now, it is believed that pesticides are important risk factor for the onset of PD. It is known that a lot of pesticides are used to simulate the characteristics of the behavior, pathology, and pathogenesis of PD in vitro and in vivo, which have provided important evidences to further study the etiology and pathogenesis of PD. Additionally, we should pay more attention to the epidemiological data of pesticide and PD. More important, we enjoy the convenience of pesticide to human life. Meanwhile, we should pay attention to carry risk assessment, to standardize the use of pesticides, and to formulate relevant laws and regulations, thus reducing diseases caused by pesticides exposure on neuron.

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Conflict of interest The authors declared that they have no conflict interest.

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Ethical Approval Ethics approval was obtained from the ethics committee of Third Military Medical University of China.

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