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Toxicity of Pesticides on CNS

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Abstract

The focus of this study is to express the toxic effect of different classes of pesticides on central nervous system. Pesticides are responsible for the neurodegenerative disorders. It can influence on ion channels such as sodium channels as well as neurotransmitters. The mode of action of pesticides include neuropathy (destruction of whole neurons), axonopathy (interfere with axon activity), myelopathy (disrupt myelination of neuron) and neurotoxicant (effect neurotransmitters such as acetylcholine). The main classes of pesticides include organophosphorus, carbamates, pyrethriods and organochlorine compounds. Organophosphate acts on the acetylcholinesterase (AChE). It can hydrolyze AChE and cause cholinergic syndromes. The symptoms of cholinergic syndromes are sweating, salivation, bronchial secretion, bronchoconstriction, mitosis, diarrhea, tremors and muscular twitching. The mechanism of toxicity of carbamate is also related to that of OPs, as it can also inhibit AChE. Pyrethroids act on electrical synapse of nerve impulse. Organochlorine compounds such as DDT disrupt the sodium channel in axonal membrane. Pesticides are responsible for Parkinson's disease. The symptoms of Parkinson's disease include loss of muscle control, trembling and absence of coordination, anxiety, constipation, dementia and depression. Farm workers, farmers and occupational exposure of pesticides are mostly diagnosed with neurodestructive disease. It is concluded that acute exposure is somehow manageable as compared to chronic exposure. More findings require educating people about dangerous activity of pesticides. Therapeutic strategies should be used to treat diseases related to pesticides. Destruction to nigrostriatal dopaminergic neurons in early life would be anticipated to result in clinical manifestations of Parkinson's disease as the individual ages. This hypothetical probability needs to be investigated in experimental animal models.

Keywords: Pesticides; Neurodegeneration; Neuropathy; Axonopathy; Myelopathy; Cholinergic syndromes; Parkinson's disease; Organophosphate; Pyrethroids; Cognitive function

Introduction

Pesticides are broadly used to increase the production of crops and protect them from dangerous pests. Pesticides are also used for household pests and garden pests. Pesticide is the main issue of discussion from the last few decades [1]. Pesticides are applied on vegetables, fruit plants and other crops etc. Almost 50 percent of fruits, vegetables and cereals grown in the world are known to comprise the pesticide remains [2]. Although pesticides are very useful but they have certain disadvantages as they contaminate our environment. They may contaminate drinking water. The total level of population treatments to pesticides is unknown, but data shows that majority of the population has noticeable concentrations of ethyl phosphate and other pesticide metabolites [1-3]. Many pesticides may act on nervous system of insect pests. Because of the resemblance of neurochemical processes, pesticides are also likely to be neurotoxic to humans. Pesticide effects are more adverse on non-target species including humans [4]. Some pesticides have mild effects such as effect on skin but others may have hazardous effects like effect on liver, lungs or brain functions. Some pesticides are neurotoxic that may upset the nervous system and interfere with the nerves' activity. Pesticides may develop neurodegenerative disease such as Parkinson's disease [1,3,4].

Neurotoxicity

Nervous system consists of brain and spinal cord. It controls all the body functions. Sensory receptor channel sends all the information to central nervous system (CNS) and impulses through motor neuron. Neurotoxins are the poisonous chemical substances that may be destructive to nerve tissues [5]. They can interfere with the activity of CNS. They may have adverse effect on CNS and can damage the brain cells [1,3,6]. Neurotoxicity can be termed as destruction of nerve cells due to some chemical, physical and biological agents. Many substances act as neurotoxic agents such as metals, industrial chemicals, natural toxins, pesticides, alcohol and other

chemicals that can affect the function both developing and mature nervous system [7]. All body systems can be affected but the brain is very sensitive to toxicity. Some neurotoxins may have immediate affect and last for few hours for example alcohol and fumes. Others may have long lasting effect for years such as effect on breathing rate and neurodegenerative disorders [6,7]. The processes like replication, migration, differentiation, myelination of neurons, and synapse formation that occur in nervous system are more susceptible to neurotoxic chemicals. Neurotoxic agents may cross the blood brain barrier and manifest qualitatively and quantitatively in developing functions of brain [6,8].

Mechanism of Action

Neurotoxicant may act in four different ways and is divided into four groups for mechanism of action of pesticides. These are:

Neuropathies

Large numbers of chemicals that are included in pesticides cause toxicity and as a result loss of neurons occurs through necrosis or by apoptosis. Such neuronal loss is irretrievable, and may result in a global encephalopathy. This is known as neuropathies. Neuropathies involve in the cause of different brain disorders like Parkinson's disease [3,7,9]. Functional losses may occur. For example a chemical MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine), which causes disintegration of dopaminergic neurons results in Parkinson's disease-like symptom. Another chemical trimethyltin acts on hippocampus, amygdala and pyriform cortex neurons, which may leads to cognitive impairment [7,9,10].

Axonopathy

The pesticides, which may act on axon of nerve cell is called axonopathy. Axonopathy causes axon destruction. Chemicals may cause chemical transaction of axon and cause axon separation from the cell body. As a result, there occurs difficulty in sensation and motor strength. A person may not feel sensation from feet and hands. For example, solvents like n-hexane and acrylamide [3,7,8,11].

Myelopathies

Those pesticides, which affect the myelination of axon of nerve cells, are called myelopathies. These chemicals may target myelin sheath and cause intramyelinic edema or demyelination [12]. However, the cell body is still in contact and so it is not structurally affected. Triethyltin and hexachlophene are examples of chemicals that are reasons for edema. As a result, formation of vacuoles starts creating a spongiosis in the brain [7,9,13].

Neurotoxicant

Neurotoxicants may interfere with neurotransmission. They can obstruct the release of neurotransmitter such as botulinum toxin, which prevents acetylcholine release, and act as competitor for specific receptors. As a result there occurs difficulty in signal transduction. This may lead to severe toxicity and may cause death of organism [10,13,14].

Types of Toxicity with respect to Exposure

There are two types of toxic effects with respect to exposure, which are given below:

Acute toxicity

Short duration of toxicity is called acute toxicity. It is caused by only single exposure of pesticides. The harmful effects on single exposure mostly have four routes such as dermal (skin), inhalation (lungs), oral (mouth), and the eyes. Acute toxicity is measured by inspecting the dermal toxicity, inhalation toxicity, and oral toxicity of test animals [10,15]. Other than these, eye and skin irritation are also examined. Acute toxicity is determined by the amount or concentration of a toxicant, which is required to kill 50 percent of the animals in a test population. This measure is usually expressed as the LD50 (lethal dose 50) [16].

Chronic toxicity

Long-term exposure to pesticides is called chronic toxicity. Any harmful effects from small repeated doses over a certain time are known as chronic effects [17]. Long-term exposure may have certain effects, which include birth defects, toxicity to a fetus, formation of benign or malignant tumors, genetic changes, blood syndromes, nerve infections, endocrine disorder, and effects of reproduction [17-19]. The chronic toxicity of a pesticide is more problematic as compared to acute toxicity to determine through laboratory examination [18,19].

Pesticides Classification

The following are the classification of pesticides:

Organophosphates

Organophosphorus (Ops) compound formed for the first time in 1940s. The chemical arrangement of OPs consists of phosphorus (P) atom bound with a double bond to an oxygen (O) or sulfur (S) and with three more single bonds to two alkoxy groups (OCH_3 or OC_2H_5) and with a leaving group. Generally, OP insecticides have sulfur bound to the phosphorus [20]. Organophosphorus acts on the acetylcholinesterase that is act on the enzymes [13,20,21]. It can hydrolyze acetylcholinesterase AChE. As acetylcholine is the major neurotransmitter so, it may cause destructive effects on central and peripheral nervous system. Inhibition of acetylcholinesterase may lead to accumulation of acetylcholine at cholinergic synapses [10,11,21]. As a result, cholinergic syndrome occurs. The symptoms of cholinergic syndromes are sweating, salivation, bronchial secretion, bronchoconstriction, mitosis, diarrhea, tremors, muscular

twitching, and various central nervous system effects. OPs may also cause intermediate syndrome in addition to acute cholinergic syndromes [13,22]. The main features of the intermediate syndrome are weakness of respiratory, neck and proximal limbs and muscles. A third neurotoxic syndrome accompanying with experience to a few OPs is organophosphate-induced delayed polyneuropathy (OPIDP). Symptoms are tingling of the hands and feet, followed by sensory loss, progressive muscle weakness and ataxia. OPIDP occurred when distal sensorimotor axonopathy established with the primary lesion in the distal part of the axon [23]. OPs can also interrupt various cellular processes such as DNA replication, neuronal survival and neurite outgrowth. It can also alter non-cholinergic pathways, induce oxidative stress and cause various behavioral abnormalities [11,13,24].

Inhibition of acetylcholinesterase: Inhibition of acetylcholinesterase is a slow but responsive process. It may depend on half-life of organophosphate. For instance, if the diethyl has half-life of 30 h, then it will be very reactive and generate serious consequences. Activation of reaction usually depends on which type of organophosphate is used [24]. Common examples of organophosphates include parathion, malathion, methyl parathion, chlorpyrifos, diazinon, dichlorvos and phosmet [24,25].

Carbamates

Carbamate insecticides originate from carbamic acid and have different degrees of acute oral toxicity that is ranging from moderate to low toxicity (carbaryl) to particularly high toxicity. The mechanism of toxicity of carbamates is related to that of OPs, as they also inhibit AChE [25]. Although, in case of carbamates inhibition is temporary and rapidly adjustable, since there is rapid recurrence of the carbamylated enzyme and carbamylated AChE does not experience the aging reaction. Moreover, the symptoms include urination, diarrhea, salivation, muscle fasciculation and CNS effects [13,15,25]. Acute intoxication of carbamates may generally resolve within few hours. Carbamates are direct AChE inhibitors and do not involve metabolic bio-activation. The treatment of carbamate intoxication depends upon the use of the muscarinic opponent atropine. Common examples of carbamates include methyl carbamate, ethyl carbamate, polyurethane [13,26].

Pyrethroids

Pyrethrin is a natural insecticide originated from yellow *Chrysanthemum cinerariifolium* and *Tanacetum cinerariifolium*. It was used in 1800s for the first time. From pyrethin, many drugs are derived to control the pest population. These synthetic drugs are known as pyrethroids. Pyrethroids are chemically stable as compared to pyrethin [13,27]. Pyrethrin and pyrethroid aerosols are often used as automated insect sprays in public areas. Pyrethroid pesticides show high toxicity to various kinds of insects and low toxicity to mammals and birds. Pyrethroids are easily degradable that is why have wide range of usage, but they have drastic effects on CNS [16,17,27]. Pyrethroids act on electrical synapse of nerve impulse. The effect is delayed closure of the inward sodium channel of the nerve membrane. Pyrethroids may also induce oxidative stress [15,28]. It can also affect various tissues and organs such as liver, brain and kidney. Pyrethroids usually divide into two classes. Type I compound produces behavioral changes such as aggressive sparring and increased startle response [29]. Type II compound has symptoms such as salivation, tremor progressing to choreoatetosis and clonic seizure a CN syndrome. The main difference between type I and type II pyrethroids is the structural difference that is presence of cyano group in type II [17,18,30]. Type II pyrethroids can also prevent GABA gated chloride channels. The process of action of pyrethroids is the same in insects and in mammals, as they bind to the sodium channel and slow its conduction. As a result stable hyperactive excitable state occurs. Important classes of pyrethroid are Allethrin, Bifenthrin Cyfluthrin, Cypermethrin, Cyphenothrin, Deltamethrin and Esfenvalerate [3,17,31].

Organochlorine compounds

The organochlorines are pesticide groups that comprise of carbon, chlorine and hydrogen. They are also denoted as chlorinated hydrocarbons, chlorinated insecticides and chlorinated synthetics. Organochlorine further divided into four major groups such as DDT (dichlorodiphenyltrichloroethane), second is cyclodienes further include (aldrin, endrin, heptachlor, dieldrin, chlordane, endosulfan and chlordecone. DDT is banned now days [31]. The third group is hexachlorocyclohexane (lindane) and the forth one is related compounds of hexachlorocyclohexane [31,32]. From the 1940s to the 1970-80s, the organochlorine insecticides were broadly used in agriculture, structure insect control, and malaria control programs. Their acute toxicity is temperate but chronic exposure may be related with damaging health effects particularly in the liver and the reproductive system [33]. Structurally DDT is a mixture of many isomers with p-DDT being reasonable for the insecticidal activity. They may disrupt the sodium channel in axonal membrane. Their function is same as that of pyrethroids [3,16,34]. They can delay the depolarization, which may leads to increased neuronal excitability. Acute exposure to high doses of DDT may leads to motor function disturbance, increased frequency of spontaneous movements, hypersensitivity to external stimuli, tremors, progressing to coarse tremors, and eventually convulsions. Signs commonly appear several hours after exposure and may cause death because of respiratory failure [35].

Cyclodiene compounds comprise of chlordane, dieldrin, aldrin, and heptachlor. These compounds were firstly used in the early 1950s. Lindane and cyclodienes have adequate to high acute oral toxicity, and their major target is the central nervous system [20,34,35]. These compounds have ability to interfere with g-aminobutyric acid (GABA) and arbitrated neurotransmission. They block the opening and thus irritating the inhibitory action of GABA. Dieldrin exposure has been related with Parkinson's disease. High-level exposure of this compound was found in prominent brain disorder that is Parkinson's disease patients. It provides possible risk for developing Parkinson's disease [36].

Parkinson's Disease

Parkinson's disease (PD) is a disabling neurodestructive disorder considered as loss of nigrostriatal dopamine neurons. PD is produced by single gene mutations (a-synuclein, parkin, DJ-1). However, genetic causes are extremely rare. Environmental factors or gene-environment interactions play a prominent role in the development of sporadic PD. Mainly pesticide exposure act as a risk factor for PD [7,15,22,36]. Although the mechanism of pesticide exposure is still not clear. However, the potential mechanism that may increase the risk for PD is through disruption of mitochondrial function. Systemic decreases of complex I of the electron transport chain have been seen in muscle, platelets and brain of PD patients. It is revealed that systemic inhibition of complex I by pesticide produce many features of PD containing selective dopaminergic disintegration, amplified oxidative damage and a-synuclein accumulation [22,36]. The symptoms of PD include loss of muscle control, trembling and absence of coordination, anxiety, constipation, dementia, depression, urinary difficulties and sleep disturbances. Only 1% of Parkinson's disease caused by genetics reasons and other 99% may be caused by environmental interaction [22,23,36].

Other Neurodegenerative Diseases

Different studies have suggested that susceptibility of amyotrophic lateral sclerosis (ALS) is related to farming as a profession. Pesticide exposure is considered as a cause of this disease. It is revealed that long-term exposure may be the cause of ALS [24,37]. ALS is caused by herbicide 2, 4-dichlorophenoxyacetic acid (2, 4-D) exposure and may cause death. Two cases of ALS have been reported after exposure to OPs and organochlorine [37,38]. Dementia is also related to pesticide exposure. Professional exposure to indefinite pesticides and fertilizers is also linked with risk of Alzheimer disease. Job-related pesticide exposure was also related with mild intellectual dysfunction in a population [39]. Alzheimer disease is the most complicated disease by the fact that the basic neurochemical defect in this disease is loss of cholinergic neurons. That is mostly caused by exposure of OPs [26,39].

Genetic Susceptibility to Pesticides Neurotoxicity

Individuals who are exposed to pesticides may be affected by polymorphisms in genes. For example, paraoxonase, an enzyme that hydrolyzes active metabolites of Ops. Some studies revealed that any change in serum paraoxonase activity modifies vulnerability to OP toxicity [40]. Paraoxonase polymorphisms affect the association of OP acquaintance in humans. It affects both erythrocyte AChE inhibition and symptom prevalence [27,28,40]. It is revealed that susceptibility depends upon measurement of serum paraoxonase activity as well as genotype [41].

Neurobehavioral Performance

The Neurobehavioral Evaluation System is used to test pesticide effects on cognitive and psychomotor function. Tests included the batteries that access memory, visuospatial processing and other aspects of intellectual function, which is mostly used to tests symbol digit, digit span, visual preservation, pattern memory, trail making and others [42]. Farmers, farm workers and pesticides applicators are exposed to multiple pesticides and so their performance is worse on tests of cognitive function [43,44]. Test that is used to detect insufficiencies in psychomotor performance is caused by impairment of sensory input, motor output, or associative delays which may include reaction time, tapping, pursuit aiming, Santa Ana tests and other pegboard tests [44,45]. Many studies revealed that results from individual tests were not fully reliable and so multiple tests should be taken in frequent way and conclude results after testing large number of population [45].

Impact of Pesticides on Society

Individuals may be frequently exposed to different pesticides and carried different nervous system defects. Pesticide poisoning may be undiagnosed, especially in farm workers with poor access to medical care and particularly in women [46,47]. That is why the workers who have never been diagnosed with pesticide poisoning may still have persistent high exposures. Effectiveness of pesticide exposure depends upon the duration of job in fields and may depend upon the concentration of pesticides [48]. Farm owners who hire others to apply pesticides may have partial personal exposure to pesticides. For example, farmworkers who have little access to information about safety practices or protective equipment may endure far more exposure than well-trained and well-appointed commercial applicators [49,50]. Even the family members of farm workers with no direct occupational exposure may be exposed at home or elsewhere [50]. Factors such as application method, use of personal protective equipment, work practices associated to hygiene, leaks, and attitudes toward risk may all affect the degree of pesticide exposure and can be combined into exposure approximations. For example, wearing gloves can increase exposure under some situations. As the fabric, gloves can become saturate with pesticide and therefore, serve as a reservoir of exposure [51]. Malaria control workers are also exposed to DDT and may have adverse effect on CNS. If a particular area is exposed to pesticides persistently then it can also contaminate water reservoirs and can also effect on large number of population [52]. As the mechanism of action of pesticides on insects as well as on mammals is the same, wide range of mammalian population may be infected with pesticides which can then lead to serious destruction in society [53,54]. Children are more affected by pesticides as compared to adults because their brain is on developing stage and if exposure of pesticides occurs on developing brain then it can cause behavioral disabilities and malfunctioning in cognitive level [55].

Conclusion

This brief summary of neurotoxicity deals with exposure to pesticides. As discussed earlier, pesticides are the most important cause for neurotoxic effects in humans. The studies also revealed that acute exposure is somehow manageable as compared to chronic exposure. Chronic exposure to low doses of particular pesticides may be responsible to the etiology of some neurodegenerative diseases (most remarkably Parkinson's disease). Developmental exposure to pesticides (both in utero and neonatally) in children may be possible and cause developmental disorders such as attention discrepancy, hyperactivity disorder, autism, or learning incapacities, needs to be further inspected. Viewing the pesticides exposure regarding the involvement of oxidative stress, more consideration is suggested to prevent the pesticide usage in the environment. Pesticides exposure results in silent neurotoxicity and may cause nervous system damage that would be obvious as a clinical condition only later in life. For instance, destruction to nigrostriatal dopaminergic neurons early in life would be anticipated to result in clinical manifestations of Parkinson's disease as the individual ages, by adding the early abuse to the normal age-linked loss of neurons. This hypothetical probability needs to be investigated in experimental animal models.

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