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EC PHARMACOLOGY AND TOXICOLOGY
Mini Review

Carcinogenic Effect of Crops Via Acetylcholinesterase Inhibition by Organophosphate

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Received: May 21, 2019; **Published:** September 30, 2019

Abstract

Numerous prejunctional inhibitory and excitatory receptors have been depicted on adrenergic nerve endings in human supply routes and veins and concentrates to date have distinguished a portion of these in human veins. The latter include muscarinic receptors in cutaneous veins which when activated by acetylcholine inhibit the evoked release of norepinephrine, and β-adrenoceptors which when stimulated by isoproterenol or epinephrine facilitate it. Human beings consider recommend that cholinergic vasodilatation can result from prejunctional restraint of adrenergic neurotransmission. The human saphenous vein appears to contain more prejunctional β-adrenoceptors than the canine, with a consequential greater enhancement of norepinephrine release when these receptors are activated. Pesticides [1] are class of synthetic chemical compounds especially manufactured to hit or retard the growth of unwanted organism destroying agricultural crop. These are especially used for the crops like mango, paddy, cotton, sugarcane and vegetable.

Organophosphates pesticides are chemically esters with the general structure $O=P(OR)_3$. They were first prepared in 1940 by Germany by using alcohols (R-OH) and phosphoric acid (H_3PO_4). In present paper the main part of the pesticide that have the carcinogenic effect has been brought to light.

Keywords: *Carcinogenic Effect; Crops; Acetylcholinesterase; Organophosphate*

Introduction

India is an agro based, developing nation facing the challenge of continuously increasing population. This creates the pressure on increasing the productivity of crops to feed such population 22% of India's GDP and 70% of net earnings of nation is dependent on agriculture production is just eaten up by pests (NABARD's Report, www.nabard.org). In spite of having high potential risk to human health, organophosphate pesticides are being used by small farmers because they are cost effective, easily available.

Many organophosphorus (OP) based compounds are highly toxic and powerful inhibitors of cholinesterase's that generate serious environmental and human health concerns [8]. Organothiophosphates with a thiophosphoryl (P=S) functional group constitute a broad class of these widely used pesticides. They are related to the more reactive phosphoryl (P=O) organophosphates, which include lethal nerve agents and chemical warfare agents, such as, VX, Soman and Sarin. Unfortunately, widespread and frequent commercial use of OP-based compounds in agricultural lands has resulted in their presence as residues in crops, livestock, and poultry products and also led to their migration into aquifers [3-5].

Organophosphate pesticides [11] are majorly used in developing countries used to kill stinging insects and beetle. These work by increasing the toxicity level in insects by retarding the activity of enzyme acetylcholinesterase as a result increasing concentration of acetylcholine neurotransmitter and cause increased activation of acetylcholine receptor. Thus, interrupting nerve impulses and killing or retarding growth of insects.

Acetylcholine receptor

An acetylcholine receptor (abbreviated AChR) is an integral membrane protein that responds to the binding of acetylcholine, a neurotransmitter [7]. Acetylcholine receptors are classified like other trans membrane receptors, according to their "pharmacology," or according to their relative affinities and sensitivities to different molecules. Although all acetylcholine receptors, by definition, respond to acetylcholine, they respond to other molecules as well.

- Nicotinic acetylcholine receptors (*nAChR*, also known as "inotropic" acetylcholine receptors) are particularly responsive to nicotine. The nicotine ACh receptor is also a Na^+, K^+ and Ca^{2+} ion channel.
- Muscarinic acetylcholine receptors (*mAChR*, also known as "metabotropic" acetylcholine receptors) are particularly responsive to muscarine.

Nicotinic and muscarinic are two main kinds of "cholinergic" receptors.

Nicotine acetyl cholinergic receptors

The major constituent of cigarettes "nicotine" capable of or having affinity to bind with nicotine acetyl choline receptor (nAchRs) [2], categorized as membrane ligand gated- ion channel. Ligands for activation of nicotine acetylcholine receptors can be either "acetylcholine" (a neurotransmitter) formed by conjunction of acetic acid and choline or nicotine. Extended binding of this endogenous neurotransmitter and nicotine from cigarette smoking can support the initiation and progression of lung cancer.

Genomic studies have suggested that variation on alleles - α5-α3-β4 of nAchRs locus on chromosome 15q24-15q25.1 is a key factor in lung cancer. There is a correlation between vulnerability to lung cancer and single nucleotide polymorphism (SNP) variation at 15q24-15q25.1. Higher risk of lung cancer sensitivity is interlinked with nAchRs variation suggested by (International Agency for Research on Cancer (Lyon France) the MD Anderson Cancer (Houston, TX, USA) and de CODE Genetics (Reykjavik, Iceland)). As chromosome 15q24-15q25.1 at this locus have 3 nicotine acetylcholine receptor (CHRNA). Studies have also suggested 30% increase in lung cancer is reported by, a non-synonymous variant, rs16969968, in CHRNAs, consequence of which is amino acid substitution (D398N) in the second intracellular loop of protein. One study in 28 squamous cell carcinoma (SCCs) of lung showed increased levels of CHRNAs and CHRNB3 transcripts together with higher acetylcholine levels which is associated with increased levels of choline acetyltransferase transcripts and decreased levels of cholinesterase transcripts.

Inhibition of acetylcholinesterase enzyme by pesticide

Cholinesterase (ko-li-nes-ter-ace) is one of many important enzymes needed for the proper functioning of the nervous systems of humans, other vertebrates, and insects. Certain chemical classes of pesticides, such as organophosphates (OPs) and carbamates (CMs) work against undesirable bugs by interfering with, or 'inhibiting' cholinesterase. While the effects of cholinesterase inhibiting products are intended for insect pests, these chemicals can also be poisonous, or toxic, to humans in some situations [6].

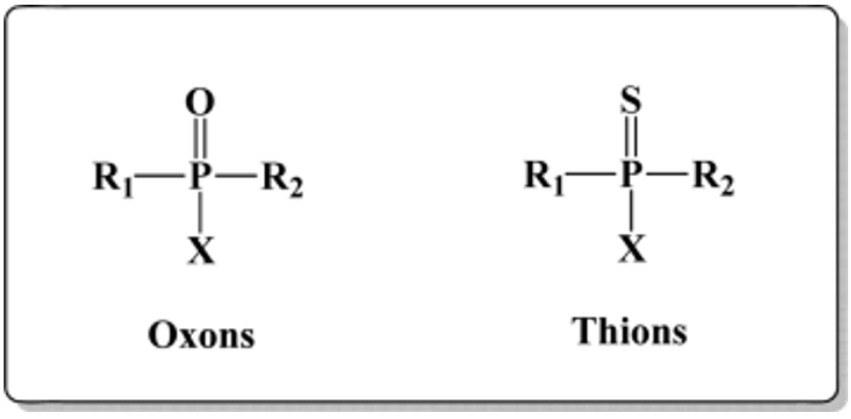
Phosphate pesticide is an agent to cause lung cancer. At chemical synapses of cholinergic receptor or neuromuscular junction acetylcholinesterase enzyme terminates the synaptic transmission or effective binding of acetylcholine at nicotinic acetylcholine receptor (nAchR) by hydrolyzing acetylcholine back into acetic acid and choline making then inactive [3].

Pesticides blocking the activity of acetylcholinesterase and terminating the hydrolysis of acetylcholine is termed as "Cholinesterase Inhibitor" [4].

Categories of cholinesterase inhibitor pesticides: Organophosphates

Cholinesterase is a family of enzymes that catalyzes the hydrolysis of the neurotransmitter acetylcholine (ACh) into choline and acetic acid, a reaction necessary to allow a cholinergic neuron to return to its resting state after activation. It involves two types:

1. Acetylcholinesterase (AChE, acetylcholine acetylhydrolase, E.C. 3.1.1.7) is found in many types of conducting tissue: nerve and muscle, central and peripheral tissues, motor and sensory fibers and cholinergic and noncholinergic fibers. The activity of AChE is higher in motor neurons than in sensory neurons [7-9]. AChE is also found in the red blood cell membranes, where it constitutes the Yt blood group antigen. The enzyme exists in multiple molecular forms, which possess similar catalytic properties, but differ in their oligomeric assembly and mode of attachment to the cell surface[9]. In the mammalian brain the majority of AChE occurs as a tetrameric, G4 form (10) with much smaller amounts of a monomeric G1 (4S) form [5].
2. Pseudocholinesterase (BuChE, EC 3.1.1.8), also known as plasma cholinesterase, butyrylcholinesterase, or acylcholine acylhydrolase, is found primarily in the liver. Different from AChE, BuChE hydrolyzes butyrylcholine more quickly than ACh [6]. Acetylcholinesterase is involved in the termination of impulse transmission by rapid hydrolysis of the neurotransmitter acetylcholine in numerous cholinergic pathways in the central and peripheral nervous systems. The enzyme inactivation, induced by various inhibitors, leads to acetylcholine accumulation, hyperstimulation of nicotinic and muscarinic receptors, and disrupted neurotransmission. Hence, acetylcholinesterase inhibitors, interacting with the enzyme as their primary target, are applied as relevant drugs and toxins [3,10].



Where,

R_1 and R_2: Substituent group

X: Organic or inorganic acid residue

Figure 1

For effective molecule substituent at R_1 should be an alkoxy group and at R_2 can be alkoxy, alkyl, alialkyl amino [3,4].

Examples- orthene, aspon, azinphos-methyl (Guthion), birlane (Chlorfenvinphos), lorsban (chlorpyriphos), delvan (dioxathion) etc.

Carbamate

In mammals and insects organophosphates and carbamates acts as neurotoxin. Accumulation of organophosphate conjugates with acetylcholinesterase in nerve endings and blood results in increased level of acetylcholine an endogenous neurotransmitter.

In absence of organophosphates [10]

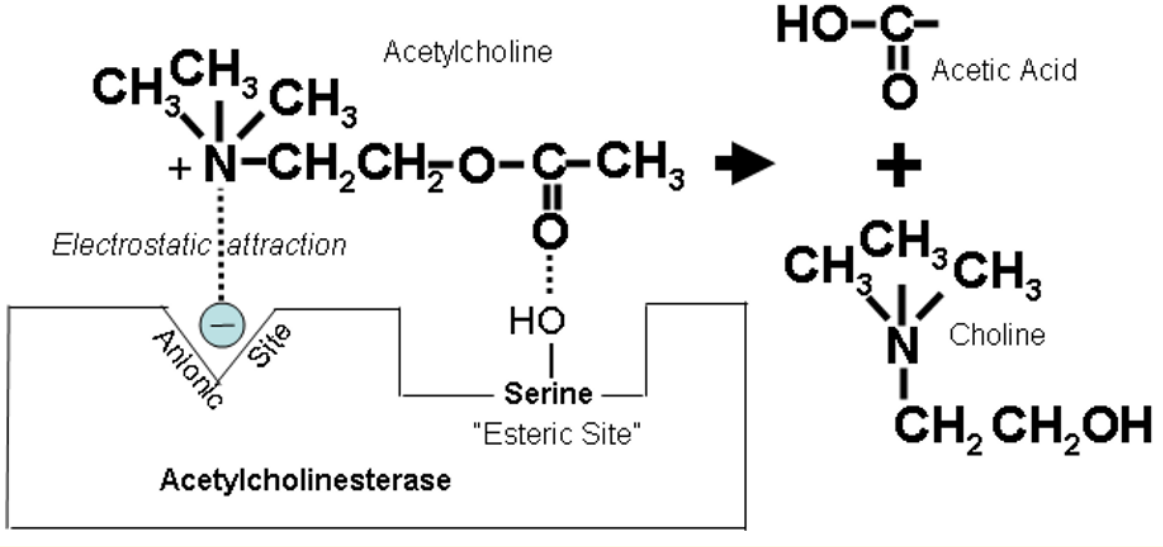


Figure 2

Organophosphates and carbamate insecticides bind to Ache and inhibit the enzyme. Allows Ache to build up [10].

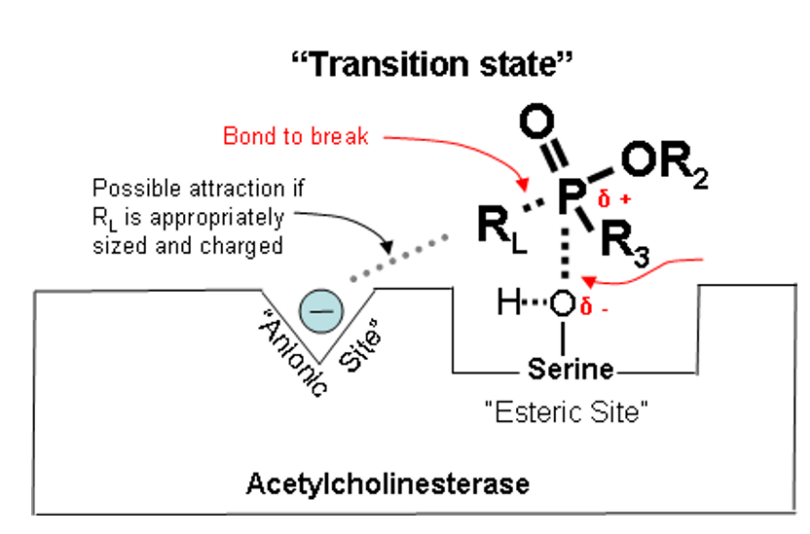


Figure 3

Conclusion

In the above explanation, it is shown that lower the level of acetylcholinesterase enzyme, higher the level of acetylcholine, higher the risk of cancer. That means phosphate pesticide is an agent to cause lung cancer. At chemical synapses of cholinergic receptor or neuromuscular junction acetylcholinesterase enzyme terminates the synaptic transmission or effective binding of acetylcholine at nicotinic acetylcholine receptor (nAchR) by hydrolyzing acetylcholine back into acetic acid and choline making then inactive. In case of failure of this mechanism or pathway, the activity of acetylcholinesterase enzyme will get abolished, which in turn will increase the level of endogenous neurotransmitter acetylcholine. Higher level of acetylcholine will prolong the binding at its receptor, which can be a causative reason for lung cancer.

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Volume 7 Issue 10 October 2019