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Review Article: The Biochemical Basis of Inorganic Insecticides: A Review

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Abstract:
Because of a growing world population, there is pressure to increase and preserve the food supply by using insecticides and other agricultural chemicals. The concept of insecticides is not new and man has been using insecticides for thousands of years to try to control these pests. An insecticide is defined under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) as any substance or mixture of substances intended for preventing, destroying, repelling or mitigating the effect of any insect including crawling and flying insects. By chemical nature, one traditional classification of insecticides places them in one of two groups: Organic and inorganic insecticides. Insecticides have also been classified based on their mode of entry and they are those that act as stomach poisons, contact poisons and fumigants. Insecticides have also been classified under the Insecticide Resistance Action Committee (IRAC) based on their mode of action and they are those that affect; the nervous system, the production of energy, the production of cuticle, the endocrine system and water balance. The mode of action of some of these inorganic insecticides are yet to be fully understood but some have been shown to affect the nervous system, energy production and water balance. Inorganic insecticides such as arsenates affect energy production in insects by replacing inorganic phosphate in the sixth step of the glycolytic pathway thereby uncoupling the ATP formation. Fluorides also affect energy production by forming a complex with phosphate and magnesium which competitively inhibits the enolase enzyme thereby uncoupling the ATP formation. Barium affects the nervous system by blocking the potassium ion gated channels which can lead to vasoconstriction, paralysis and death eventually. Mercury and phosphine also affect the nervous system by inhibiting acetylcholinesterase resulting to hyperactivity and death eventually. Boric acid, silica aerogels and diatomaceous earth affect water balance in insects by absorbing lipids from the outer layer of the insect's exoskeletons causing it to dehydrate.

1.0. Introduction:

Humanoids have been on earth for more than 3 million years, while insects have existedfor at least 250 million years. The first materials likely used by ourprimitive ancestors to reduce insect annoyance were mud and dust spread over their skinto repel biting and tickling insects, a practice resembling the habits of elephants, swine,and water buffalo. Under these circumstances, mud and dust would be classed asrepellents, a category of insecticides (Ware, 2000).

Historians have traced the use of pesticides to the time of Homer around 1000 B.C., butthe earliest records of insecticides pertain to the burning of "brimstone" (sulphur) as afumigant. Pliny the Elder (A.D. 23-79) recorded most of the earlier insecticides were used in their natural state. Included among these were the use of gall from a green lizard to protectapples from worms and rot. Later, there were variety of materials used with questionableresults: extracts of pepper and tobacco, soapy water, whitewash, vinegar, turpentine, fishoil, brine, lye and many others (Ware, 2000).

At the beginning of World War II (1940), insecticide selection was limited to severalarsenicals, petroleum oils, nicotine, pyrethrum, rotenone, sulphur, hydrogen cyanide gas,and cryolite. And it was World War II that opened the Chemical Era with the introduction of a totally new concept of insect control chemicals--synthetic

organicinsecticides, the first of which was DDT (Sarwar and Salman, 2015).

Insecticides are substances which are intended for preventing, destroying, repelling or mitigating the effect of any insect including crawling and flying insects. Insecticides also destroy the insects' eggs and larvae. These are called ovicides and larvicides respectively (Achudume, 2012).

By chemical nature, one traditional classification of insecticides places them in one of two groups: Organic and inorganic insecticides. Organic insecticides are based on chemicals having carbonas the basis of their molecular structure. Inorganic insecticides do not contain carbon and are often derived from mineral ores or their salts (Sarwar, 2016).

Biochemical basis of inorganic insecticides refers to the biochemical reaction or mechanism or the mode of action of inorganic insecticides. Insecticides have also been classified under the Insecticide Resistance Action Committee (IRAC) based on their mode of action and they are; the nervous system, the production of energy, the production of cuticle, the endocrine system and water balance (IRAC, 2005). The mode of action of some of these inorganic insecticides are yet to be fully understood (Sarwar, 2015) but some have been shown to affect the nervous system, energy production and water balance (Casida, 2009).

It is evident that insecticides have been used to boost food production to a considerable extent and to control vectors of disease. However, these advantages that are of great economic benefits sometimes come with disadvantages when subjected to critical environmental and human health considerations (Sarwar, 2015).

1.1. Inorganic Insecticides that affect the Production of Energy

These inorganic insecticides poison the glycolytic pathway by taking over the binding and active sites of the enzymes that catalyse substrates in the glycolytic pathway.

The poisons include;

- Arsenate
- Fluoride

1.1.1. Arsenates:

Arsenates (AsO_4^{3-}) are salts or esters of arsenic acid. Arsenate resembles phosphate in manyrespects, since arsenic and phosphorus occur in the same group (column) of the periodic table (Drahl, 2012). Arsenate can replace inorganic phosphate in the step of glycolysis that produces 1,3-bisphosphoglycerate from glyceraldehyde 3-phosphate. This yields 1-arseno-3-phosphoglycerate instead, which is unstable and quickly hydrolyses, forming the next intermediate in the pathway, 3-phosphoglycerate and arsenate. This is how 3-phosphoglycerate forms without the generation of an ATP molecule. This event keeps happening in a cyclic manner. Released Arsenate reacts back with the glyceraldehyde-3-phosphate and ATP production is skipped. Therefore, Arsenate poisoning uncouples the ATP formation in the glycolytic pathway and the result is that there is no net production of ATP (*Hughes*, 2002).

Normally, each glucose molecules leads to the production of 4 ATP molecules; (i) 2 ATP molecules formed during the conversion of 1,3-bisphosphoglycerate to 3-phosphoglycerate and (ii) 2 ATP molecules forms during the conversion of phosphoenolpyruvate to pyruvate. However, two molecules of ATP are spent; one at phosphorylation of glucose molecule and one at phosphorylation of fructose-6-phosphate (Piszczatowski *et al.*, 2014).

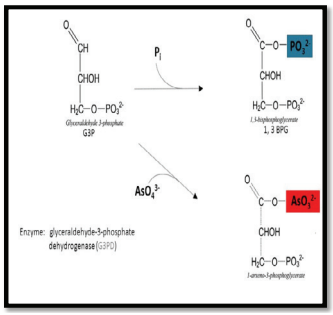

Fig 1: 6th step of glycolysis and the action of arsenate.

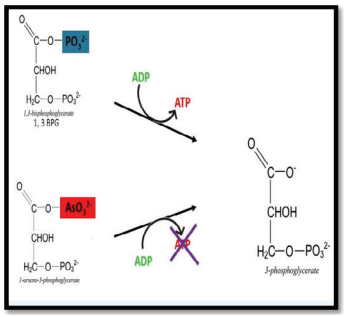

Fig 2: 7th step of glycolysis and the consequent action of arsenate.

Source: (Lai, 2005).

1.1.2. Flouride

Fluoride is the simplest anion of fluorine. Its salts and minerals are important chemical reagents and industrial chemicals, mainly used in the production of hydrogen fluoride for fluorocarbons *(Raghunathan et al.,* 2014*)*.

Enolase is also known as phosphopyruvate hydratase. The chemical reaction catalysed by enolase is:

2-phospho-D-glycerate ⟶ phosphoenolpyruvate + H2O.

Mg^{2+} works by binding to the enzyme at the active site and producing a conformational change. This makes it possible for the substrate (2-PG) to bind at the enolase active site. Once this happens, a second metal ion, Mg^{2+}, comes in and binds to the enzyme to activate the enolase catalytic ability (Jung *et al.*, 2013).

This Mg^{2+} dependent dehydration reaction is inhibited by fluoride. Fluoride is a known competitor of enolase's substrate 2-PG. It is believed to bind and form a complex with phosphate and magnesium and prevents the formation of the metal-bridge enzyme-substrate complex (E-M-S) necessary for enolase action (Jung *et al.*, 2013). The phosphate ion binds in the same site as the phosphate group of the substrate/product (2-PG/PEP), and induces binding of catalytic Mg^{2+} ion. The fluoride and the magnesium ions interact with the structural and catalytic subunits of the enzyme. These fluoride ions positions correspond closely to the substrate's carboxylate moiety, thus inhibiting the binding of the substrate (2-PG) (Qin *et al.*, 2008).

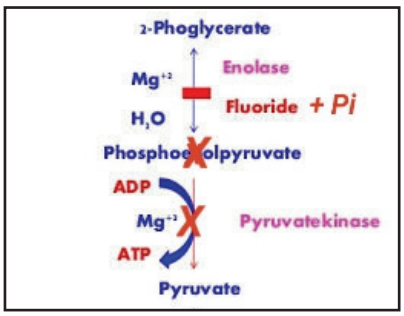

Fig 3: Inhibition by Fluoride.
(Retrieved from https//www.slideshare.net/mobile/YESANNA/glycolysis-42953283).

1.2. Inorganic Insecticides that affect the Nervous System

1.2.1. Barium

In low doses, barium ions act as a muscle stimulant, and higher doses affect the nervous system, causing cardiac irregularities, tremors, weakness, anxiety, shortness of breath, and paralysis. This toxicity may be caused by Ba^{2+} blocking the potassium ion gated channels, which are critical to the proper function of the nervous system (Patnaik, 2003). Barium stimulates striated cardiac and smooth muscle, regardless of the innervation. It is antagonistic to all muscle depressants, no matter whether they act primarily on nerve or muscle. Initial stimulation of contraction leads to vasoconstriction through direct action on arterial muscle, peristalsis through action on the smooth muscle, tremors and cramps through on the skeletal muscle. If dose is sufficient, stimulation is followed by weakness and eventually by paralysis of the different kinds of muscle (Hayes *et al.*, 1991).

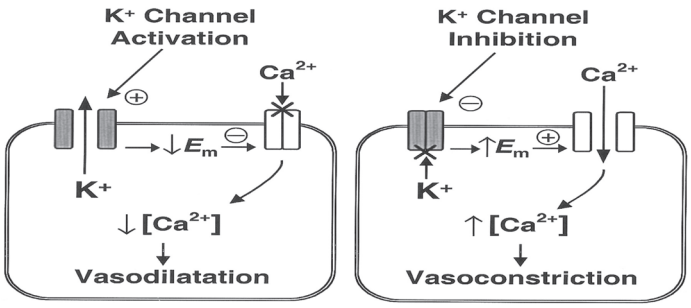

Fig 4: Vascular smooth muscle response to k+ gated channel activation/inhibition (Sobey, 2001).

1.2.2. Mercury

Mercury is a chemical element with symbol Hg and atomic number 80. It is commonly known as quicksilver and was formerly named hydrargyrum. It is a heavy metal that has been used for centuries as a medicine and a poison. Mercury can exist in different chemical states or compounds (Achudume, 2012).

Acetylcholine is one of the main neurotransmitters that nerves use to control muscle movement. After release, acetylcholine must be degraded in order to stop the "go" signal from continuing to stimulate the receiving cell. Acetylcholine is degraded by an enzyme called acetylcholinesterase. This enzyme is found in the synaptic cleft, which is the space between the "fingertips" of a nerve cell and the neighboring cell that the nerve activates. Mercury inhibits this enzyme differently in different species, depending on whether it can easily find a sulfhydryl group to latch onto. For human acetylcholinesterase, it takes millimolar amounts of mercuric chloride ($HgCl_2$) to inhibit the enzyme (Frasco *et al.*, 2007).

1.2.3. Phosphine (PH_3)

Phosphine (PH_3) was discovered in the late 1700s and has been used as a grain fumigant since the 1930s. It is by far the dominant means of controlling pest insects in stored grain and many other stored commodities. Despite the importance of phosphine to global food security, the mechanisms by which it acts are not understood (Nath *et al.*, 2011). Phosphine is widely used as a fumigantas it is gaseous above −88°C with a density of 1.17 times that of air, which allows it to disperse readily during fumigation. Phosphine is highly toxic to aerobically respiring organisms, but not to anaerobic or metabolically dormant organisms. Thus, it can be used to kill insect pests in grain, without affecting grain viability (Chaudhry *et al.*, 1997).

There is evidence that phosphine increases acetylcholine neurotransmission by suppressing acetylcholinesterase (Shadnia *et al.*,2009). Because acetylcholine is an excitatory neurotransmitter and the role of the esterase is to attenuate acetylcholine signalling, exposure to phosphine would be expected to inhibit the attenuation. The net result would be overactive acetylcholine signalling, which would most likely be expressed as hyperactivity and in extreme cases, excitotoxicity. There is direct evidence that acute phosphine exposure leads to a decrease of insect acetylcholinesterase activity, both *in vitro* and *in vivo*, though the *in vitro* concentration of phosphine that was used was quite high (Nath *et al.,* 2011).

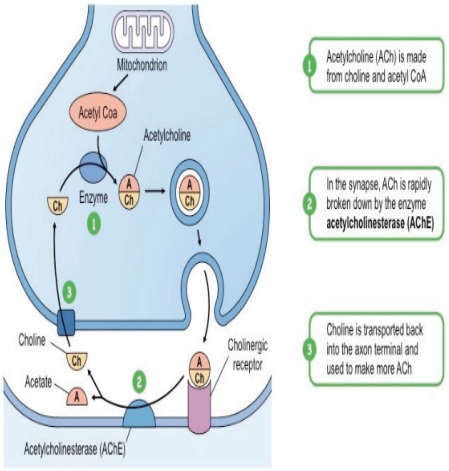

Fig 5: Acetylcholinesterase in the cleft. (Retrievedfromhttps://peaknootropics.com/acetylcholinesterase-memory-problems).

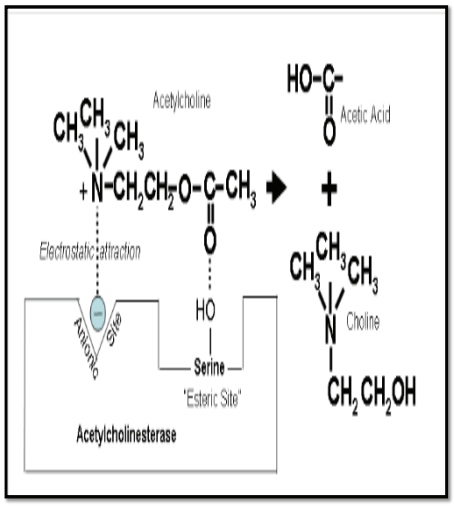

Fig 6: Chemical structure of Acetylcholinesterase. (Retrieved from https://www.atsdr.cdc.gov/csem).

1.3. Inorganic Insecticides that affect water balance

They are used as insecticides due to their abrasive and physico-sorptive properties. The fine powder absorbs lipids from the waxy outer layer of insect's exoskeletons, causing them to dehydrate. They include:

- Boric acid
- Silica aerogels
- Diatomaceous earth

1.3.1. Boric Acid

Boric acid (H_3BO_3) also called hydrogen borate, boracic acid, orthoboric acid and *Acidumboricum*, is a weak, monobasic Lewis acid of boron often used as an antiseptic, insecticide, flame retardant, neutron absorber, or precursor to other chemical compounds. It exists in the form of colorless crystals or a white powder that dissolves in water. It has been used as an ant bait ingredient, but can cause phytotoxicity when applied to the landscape (Sarwar, 2016). It is generally considered to be safe to use in household kitchens to control crawling household insects and ants and its quite useful in the control of all cockroach species when placed in wall voids and other protected, difficult-to- reach sites (Achudume, 2012). It is believed to act as a stomach poison affecting the insects' metabolism in a way that is yet to be elucidated, and the dry powder is abrasive to the insect's exoskeletons (Perelygin *et al.*, 2006).

1.3.2. Silicaaerogel

Silica gels or silica aerogels-light, white, fluffy, silicate dusts used for household insect control. The silica aerogels kill insects by absorbing waxes from the insect cuticle, permitting the continuous loss of water from the insect body, causing the insects to become desiccated and die from dehydration (Ware, 2000). This material also has a tremendous surface area which explains why it is a good absorbent (El-bendary and El-Helaly, 2013).

1.3.3. Diatomaceous Earth

Diatomites are formed by the accumulation of the amorphous silica (opal, $SiO_2 \cdot nH_2O$) remains of dead diatoms (microscopic single-celled algae) in lacustrine or marine sediments. In order to be effective as an insecticide, diatomaceous earth must be uncalcinated (i.e., it must not be heat-treated prior to application) and has a mean particle size below about 12 micrometers (Capinera, 2008). Diatomite is used as an insecticide, due to its abrasive and physico-sorptive properties. The fine powder absorbs lipids from the waxy outer layer of insect's exoskeletons, causing them to dehydrate. It is commonly used in lieu of boric acid, and can be used to help control and possibly eliminate bed bug, house dust mite, cockroach, ant and flea infestations. This material has wide application for insect control in grain storage (Sarwar, 2016).

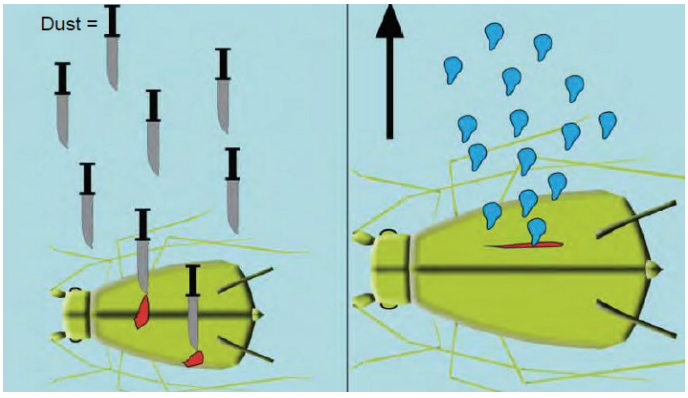

Fig 7: Abrasion of the cuticle by abrasive dusts. (Ryan, 2007)

1.4. Conclusion

Tremendous benefits have been derived from the use of insecticides in agriculture, forestry, public health and the domestic spheres. The drawback for many of these products are their high rates of application, lack of selectivity and phytotoxicity. The earliest insecticides are inorganic substances such as sulphur, mercury, lead and arsenic, and some of these inorganic insecticides are still in use today. Inorganic insecticides do not contain carbon and are often derived from mineral ores (mercury) or their salts (mercury chloride). Most insecticides that have carbon in their chemical structure are made from petroleum-based compounds. Some insecticides (boric acid, silica dioxide or diatomaceous earth/ D.E.) do not contain carbon and so they are technically inorganic molecules. The Integrated Pest Management (IPM) program encourage a limited use of agrochemicals the other use of other methods of pest management such as mechanical and biological control. Today the pest management toolbox has expanded to include use of genetically engineered crops designed to produce their own insecticides or exhibit resistance to broad spectrum products or pests.

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