(Ent-714) Insecticide Toxicology Credit Hours 3(2-1)

Lecture # 7 Delivered by Dr. Hassan Yasoob

Topic- Mechanism of Action of Major Groups of Insecticides

Insecticides plays a pivotal role in pest management, Mode of action of insecticides is very important toxicological aspects to be clearly understood to develop a strategic plan against pests. Repeated application of insecticides with similar mode of action inflected several vulnerable issues like resistance, resurgence, reduced sensitivity etc. Decades ago insecticides generated broad spectrum activity irrespective of insect; mortality in exposed insect or showed toxicity after entry in the body. Several environmental factors like non-target insect mortality, toxicity towards beneficial insects leads to development of site specific insecticides. Several bio rational insecticides derived from natural resource with novel mode of action. Receptor based modulators or inhibitors regulating the ion flow to the nervous system are introduced. Insecticide Resistance Action Committee (IRAC) categorises insecticide mode of action in 30 different categories and grouped the insecticides accordingly. Changing the moiety pattern of the parent molecules next generation insecticides of the particular group is introduced with the specific mode of action. Functioning of the molecules to the target site determines its nature of action and makes them effective to particular target insects.

Insecticides are agents or tools of chemical or biological origin that manage or control insects significantly; control may result from killing the insect or otherwise preventing it from engaging in behaviors believed to be destructive. The insecticides may be applied in myriad of formulation (EC, WP, WDG, OD, SL, D, G etc) and delivery systems (baits, sprays, dusting or slow release diffusion etc). Insecticides act on the target pest in various ways by targeting either a specific system or may affect in broad spectrum. The way by which an insecticide interferes with the biological process of target pest is called mode of action. There are several different mechanisms or way by which insecticides works.

Nevertheless, mode of action is the most important tool for ensuring sustained ability to control insect pests. The earliest records of insecticides pertain

to the burning of "brimstone" (sulfur) as a fumigant. Later, we find a variety of materials used with questionable results like extracts of pepper and tobacco, soapy water, whitewash, vinegar, turpentine, fish oil, brine, lye among many others was used to control insect. At the beginning of World War II (1940), our insecticide selection was limited to several arsenicals, petroleum oils, nicotine, pyrethrum, rotenone, sulfur, hydrogen cyanide gas, and cryolite. Modern Era of Chemical control began after World War II with the advent of synthetic organic insecticides, following the discovery of insecticidal property of DDT by Paul Muller dramatic shift of pest management was occurred during the period (1940). The momentum of these inventory encouraged further efforts in the development of synthetic insecticides in the following 20 years. Subsequently era of organophosphates, carbamates and pyrethroids started and commercialized in the arena of insect control. The persistence nature of organochlorines led to global distribution and accumulation in the biota with serious consequences. "Silent Spring" by Rachel Carson during 1962 aroused the public concern about the harmful impacts of pesticides [1]. In earlier days the insecticides acts in broad spectrum way; no target specificity was belonging to those chemistry and as a result impact on insect as well as environment was vast and acute. To eliminate the negative impact of insecticides like persistence and environmentally unsafely or hazardous effect on non-target organisms, resistance, resurgence and residue thrust has led to develop insecticides with target specificity or novel mode of action. Simultaneously insecticide from plant origin or fermented chemical compound produced from soil actinomycetes or sea annelids or highly potent chitin synthesis inhibitor or receptor based agonist or antagonist molecules have been developed. Effective pest management always relies-on broad knowledge about the pesticide chemistry and their mode of action and related toxicological facts associated to any pesticides. IRAC (Insecticide Resistance Action Committee) designed or classified insecticides according to their mode of action those are acting at target site where mutation could confer cross resistance to all compounds share same site of action.

Botanicals

(1) Nicotine: Nicotine represents a class of alkaloid, a chemical class of heterocyclic compounds "nicotinoids" is extracted by several methods from tobacco, and is effective against many types of insect pests, but is used particularly for aphids, caterpillars and soft bodied insects.

Mode of Action

Nicotine interacts with acetylcholine (ACh) receptors at the central nervous system results in twitching, convulsions, and death. Nicotine does not act as an acetylcholinesterase inhibitor.

Rotenone

(2) Rotenone

Rotenone or rotenoids are produced from roots of two genera of the legume family: Derris and Lonchocarpus grown in South America. It is both a stomach and contact insecticide and used for the last century and a half to control leaf-eating caterpillars.

Mode of Action

Rotenone is a respiratory enzyme inhibitor, interfere with NAD+ (a coenzyme involved in redox reaction in metabolic pathways) and coenzyme Q (a respiratory enzyme responsible for carrying electrons in some electron transport chains), resulting in failure of the respiratory functions

(3) Pyrethrum

Pyrethrum is made from dried and powdered flowers of chrysanthemum (C. cinerariaefolium). Pyrethrins are ester formed by combination of chrysanthemic acid and pyrethric acid with three rethronoles viz. pyrethrolone, cinerolone and jasmolone. The esters of chrysanthemic acid are pyrethrin I, cinerin I and jasmolin I; whereas the esters of pyrethric acid include pyrethrin II, cinerin II and jasmolin II

Mode of Action

Pyrethrum offers rapid knockdown action which in many cases is reversible. Pyrethrum is an axonic poison, as are the synthetic pyrethroids and DDT. Pyrethrum have greater insecticidal effect when the temperature is lowered, a negative temperature coefficient, as of DDT. They affect both the peripheral and central nervous system of the insect. Pyrethrum initially stimulates nerve cells to produce repetitive discharges and eventually

cause paralysis. Pyrethrum interferes with sodium channel along the length of nerve cells and cause excitation.

(4) Limonene or d-Limonene

Limonene belongs to a group often called florals or scented plant chemicals. Extracted from citrus peel, it is effective against external pests of pets including fleas, lice, mites, and ticks, and is virtually nontoxic to warm-blooded animals.

Mode of Action

It affects the sensory nerves of the peripheral nervous system, but it is not a ChE inhibitor.

(5) Neem

The main neem chemical is a mixture of several related compounds belonging to tetranortriterpenoid or limonoids like azadirachtin, meliantriol, salanin, nimbin and nimdidin and others. Azadirachtin has shown some rather sensational insecticidal, fungicidal and bactericidal properties, including insect growth regulating qualities.

Mode of Action

Azadirachtin is structurally somewhat similar to insect hormones ecdysones and seems to be ecdysone blocker thus it disrupts molting by inhibiting biosynthesis or metabolism of ecdysone, the juvenile molting hormone.

(6) Organochlorines

The organochlorines or chlorinated hydrocarbons are insecticides that contain carbon (thus organo-), hydrogen, and chlorine combined with oxygen ancluding a number of Cl-Cl bond, absence of very reactive intramolecular sites and presence of carbon ring structures including benzene ring, high lipophilicity and apolarity.

DDT

1, 1'-(2, 2, 2-Trichloroethane-1, 1-diyl) bis (4-chlorobenzene) synthetically produced by Othmar Zeidler in 1874 and Paul Muller in 1939 discovered the insecticidal property which brings revolution in pest management science. Pure DDT is a white, odourless tasteless crystalline solid.

Mode of Action

DDT is potent broad spectrum insecticides also toxic to mammals, fish and birds. Symptom of poisoning indicates that the main site of action is nervous system. DDT poisoning results in the characteristic "repetitive discharge". Yeager and Munson in the year of 1942 mentioned that multiplication effect of a single impulse on DDT treated nerve. In insects it opens sodium ion channels in r-urons, causing them to fire spontaneously which leads to spasm eventually death. Welsh and Gordon pointed out that the phenomenon of increased spontaneous discharge in the central nervous system and synaptic transmission as similar to hypocalcemia (reduction in the levels of Ca2+ or Mg2+ ions) in the perfusing fluid. Another theory related to DDT action states that lipophilic nature of DDT allows to concentrate in the cell membrane and affect the function of membrane proteins. The major mechanism by which DDT acts is thought to be by prolonging the opening of membrane bound Na+ channel. DDT is negatively correlated with temperature and thus much toxic in cold blooded than warm bodied.

(7) Lindane

Michael Faraday synthesized the compound in 1825. There are seven different isomers of HCH, the ɣ isomer possessed the insecticidal property which was discovered in 1940. HCH known as benzenehexachloride (BHC). Consequently, the gamma isomer was isolated, produced and sold as odorless insecticide lindane. In contrast, technical grade HCH has a strong musty odor and flavor. Because of its very low cost, HCH is still used in many developing countries.

Mode of Action

The effect of HCH resembles with DDT. Lindane is a neurotoxin that interferes with GABA gated chloride channel complex at the picrotoxin binding site. Effect of lindane is much faster than DDT; within hours treated insect shows tremors and convulsions leading to prostration.

(8)Cyclodiene

Cyclodienes are chlorinated insecticides prepared by diene-synthesis or Diels-Alder reaction. Highly active insecticides having long persistency in soil and relatively stable to the ultraviolet rays of sunlight, thus now the use is restricted. The compounds are all cyclic, however only a few of them are dienes. Cyclodiene include chlordane, heptachlor, aldrin, toxaphene, endrin, Isodrin, dieldrin, endosulfan and mirex.

Mode of Action

Like most of the chlorinated hydrocarbon insecticides cyclodiene compounds mainly act as neurotoxicants. Cyclodienes have a positive temperature correlation--their toxicity increases with increasing ambient temperature unlike DDT and BHC. An important difference between the mode of action of DDT and BHC is cyclodienes readily absorbed by insect skin. Cyclodienes usually interferes with the GABA (g-aminobutyric acid) gated chloride channel like BHC. This receptor operates by increasing chloride ion permeability of neurons. Cyclodiene cause an excessive release of acetylcholine at presynaptic site but they do not interfere with the function of acetylcholinesterase enzyme in target site. However there are evidence regarding interference of cyclodienes to ATPase from nerve chord and muscle. Infected insect showed pronounced rate of respiration, symptom of poisoning shows strong tremorsband short trains of impulses.

(9) Organophosphates

The organophosphate compounds are neutral ester or amide derivates of phosphorus acids carrying a phosphoryl (P-O) or thiophosphoryl (P-S) groups. Most of the OP conforms the general structure $(RO)_2P(A)X$. Where R is ethyl or methyl, A is sulfur or oxygen and X can vary a great deal. Their

insecticidal qualities were first observed in Germany during World War II in the study of the extremely toxic OP nerve gases sarin, soman, and tabun. Initially, the discovery was made in search of substitutes for nicotine, which was heavily used as an insecticide. The OP compounds have two distinct characteristic features: firstly they are generally toxic to vertebrates and secondly they are chemically unstable or non-persistent in nature, readily biodegradable by means of microbes activity. This particular quality of OP compounds leads to become preferable over OC and cyclodienes. About 100 insecticides of technical grade are commercialized in world.

Mode of Action

The main site of action is nervous system by acts upon cholinesterase, an enzyme that plays a pivotal role in hydrolyzing acetylcholine. Actylcholine is a neurotransmitter that upon releases from neuron stimulates the opening of Na^+ and K^+ channel that regulates the function of brain. Acetylcholine signaling in the synapse is terminated with the act of AchE, which catalyze the hydrolysis of acetylcholine to form inactive acetate and choline. The enzyme is said to be phosphorylated by the P atoms to the esteric site when it becomes attached to the phosphorous moiety of the insecticide, a binding that is irreversible. This inhibition results in the accumulation of acetylcholine (ACh) at the neuron/neuron and neuron/muscle (neuromuscular) junctions or synapses, causing rapid twitching of voluntary muscles and finally paralysis.

(10) Carbamates

The carbamate insecticides are derivatives of carbamic acid typically having some kind of aryl substituent as the leaving group. The first derivative of carbamic acid (Physostigmine) was derived from the Calabar beans, Physostigma venenosum. Stedman elucidated the structure of physostigmine and also synthesized synthetic analogues of methylcarbamates some of which showed toxicity to many insect species. And like the OPs, their mode of action is inhibition of cholinesterase (ChE) enzyme.

Mode of Action

Carbamate insecticides inhibit cholinesterase (ChE) as OPs does resulting in the accumulation of acetylcholine in the nerve synapse.

Carbamate reacts with the serine hydroxyl group within the enzyme active site resulting in carmamylation of this hydroxyl group and yielding a hydroxylated "leaving group". This process inactivates the enzyme and blocks the degradation of acetylcholine, and they behave in almost identical manner in biological systems, but with two main differences. Some carbamates are potent inhibitors of aliesterase (miscellaneous aliphatic esterases whose exact functions are not known), and their selectivity is sometimes more pronounced against the ChE of different species. Second, ChE inhibition by carbamates is reversible (carbamylated). The only cholinergic synapses known in insects are in the central nervous system. (The chemical neuromuscular junction transmitter in insects is thought to be glutamic acid.)

(11) Pyrethroids

Use of pyrethrum was recorded since 400 BC being an agent of louse control, during 1967 powder of pyrethrum use as insecticide was also recorded. Originally pyrethrum (dried flower of Chrysanthemum cinerariaefolium) marketed as fine powder, but its use for agricultural purpose was low being of its cost and instability in sunlight. For field efficacy improvement of pyrethroid photostability was necessary. The first synthetic modifications of the structure of pyrethrins mainly involved changes of the alcohol moiety. Allethrin, the first synthetically produced rather derived from pyrethrin I during 1949. In recent decades, many synthetic pyrethrin-like materials have become available. They were originally referred to as synthetic pyrethroids. Modification of pyrethrin compound was done up to fourth generation.

Mode of Action

Pyrethroids have rapid paralytic action on insect; it share similar modes of action, resembling that of DDT, and are considered axonic poisons. The two type of pyrethroids prolong the sodium current keeping open the sodium channel during excitation, causing depolizing after potential. When the after potential exceeds the membrane threshold repetitive action potential generated leading to hyperexcitation. Type I, among other physiological responses, have a negative temperature coefficient, resembling that of DDT.

Type II, in contrast have a positive temperature coefficient, showing increased kill with increase in ambient temperature. Pyrethroids affect both the peripheral and central nervous system of the insect. The stimulating effect of pyrethroids is much more pronounced than that of DDT.

(12)Nicotinoids

The nicotinoids are a newer class of insecticides with a new mode of action. The term "neonicotinoids" was derived to indicate to those chemical compounds share the same features with nicotinoids, but with an additional feature: the partial positive charge on the nitrogen atom conferred by the neighbouring electron withdrawing group. They are also called chlorinated insecticides. They have been previously referred to as nitro-quanidines, neonicotinyls, neonicotinoids, chloronicotines and more recently as the chloronicotinyls. This group of insecticides is systemic in nature also sharing notable contact and stomach action, mostly effective against sap feeders as well as showed toxicity against chewing insect also. Imidacloprid and acetamiprid are the first commercial neonicotinoids developed. Later on several neonicotinoid insecticides developed and marketed.

Mode of Action

Nicotine and the nicotinoids mimic the action of acetylcholine(excitatory neurotransmitter in the CNS), readily interact with theacetylcholine binding site of the nicotinergic acetylcholine receptors(nAChR) act as agonist. The interaction causes excitation and paralysis.

(13)Avermectins

Avermectins are series of eight related pentacyclic lactones that contain a disaccharide of methylated deoxysugar oleandrose, including anthelminthics like ivermectin, abamectin, selamectin and doramectin. Avermectin was derived from fermented broth of soil actinomycetes Streptomyces avermitilis, which possesses insecticidal, acaricidal properties. Abamectin is the common name assigned to the avermectins, a mixture of containing 80% avermectin B1a and 20% B1b, homologs that have about equal biological activity.

Emamectin benzoate is an analog of abamectin widely commercialized. Milabectin (miticide with activity on piercing/sucking insects) has been introduced and commercialized.

Mode of Action

Avermectins acts as agonist of gamma-aminobutyric acid (GABA) gated chloride channel that eliminated the GABA inhibitory postsynaptic potential as well as excitatory potsynaptic potentials at the neuromuscular junction in insects and mites. Behavioral changes such as feeding, delay in egg lying; though death may not occur for several days.

(14) Fiproles

Member of phenylpyrazoles, discovered in 1987 and introduced in 1993 in India. It is a broad spectrum insecticide with contact and stomach activity. Fipronil is used for the control of many soil and foliar insects. Fipronil is effective against insects resistant or tolerant to pyrethroid, organophosphate and carbamate insecticides.

Mode of Action

Fipronil is potent nerve poison that blocks the (g-aminobutyric acid-(GABA) regulated chloride channel in neurons, thus antagonizing the "calming" effects of GABA, similar to the action of the Cyclodienes.

(15) Indoxacarb

Indoxacarb, indeno oxadiazine are broad spectrum insecticides effective against lepidopteran larvae having both larvicidal and ovicidal action.

Mode of Action

Indoxacarb inhibits sodium ion entry into the nerve cells which results in impaired nerve function, cessation of feeding, paralysis and death of target pest species. It is also a pro-insecticide that is bioactivated by esterases inside the insect following ingestion and cuticular absorption. The rate of bioactivation of insecticide is more in lepidopteran insects. Its low impact on human health, low toxicity to non-target organisms (birds, fish and plants), low potentials for ground water contamination, lower rates, low pest resistance potential has made it compatible with integrated pest management programmes.