MODES AND MECHANISMS OF ACTION OF INSECTICIDES

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Insecticide Entry Routes into Insects

Insect toxicology is part of a much broader field, pharmacology and toxicology, in which studies of drug action are known as pharmacodynamics. Study of the actions of insecticides may therefore be called the pharmacodynamics of insecticides, or simply the pharmacology of insecticides.

Its existence is necessitated by:

(1) The need for therapeutic measures for accidental poisoning

(2) The demand for logical explanation of these toxic actions and of their subsequent side effects in beneficial animals as well as man

(3) The realization that it can provide a logical basis for developing even more useful compounds and can help in understanding the normal physiology and biochemistry of animals.

The insecticide is generally termed “**Selective toxicity**" generally refers to cases where mammals are less affected by a toxicant than insects and other pests.

It is, however, equally appropriate to use the term in the cases where a beneficial species of insect is unharmed by an insecticide while pest species are killed.

Intra- and interspecific differences in susceptibility to various kinds of insecticides are increasingly drawing more attention.

Both the modes of action of insecticides and the differences in responses of various organisms also helps in understanding the intricate differences In their physiology and biochemistry.

Classification Of Insecticides By Their Actions

Brown (1951) has classified insecticides into five groups, based on mode of action:

(I) Physical poisons
(2) Protoplasmic poisons
(3) Respiratory poisons
(4) Nerve poisons
(5) Poisons of a more general nature.

Most modern insecticides are nerve poisons, and Brown's classification still covers almost all insecticides marketed today.

Another way of grouping the insecticides is to separate them into three groups according to mode of entry:

(1) stomach poisons

(2) contact poison

(3) fumigants

This approach, though often very useful as a means to describe an insecticide to non-experts, has some technical limitations such as the problem of having to classify a multipurpose insecticide as belonging to more than one category.

TABLE 4-1. A Classification of Insecticides on the Basis of Their Mode of Action

Groups	Subgroups	Examples
Physical poisons[a]	—	Heavy mineral oils, inert dust
Protoplasmic poisons[a]	—	Heavy metals, e.g., Hg, acids
Metabolic inhibitors	Respiratory poisons[a]	HCN, CO, H_2S, rotenone, dinitrophenols
	Inhibitors of mixed-function oxidase	Pyrethrin synergists
	Inhibitors of carbohydrate metabolism	Sodium fluoroacetate
	Inhibitors of amine metabolism	Chlordimeform
	Insect hormones	Juvenile hormone analogues
	Inhibitors of chitin synthesis	Diflubenzuron

Table 4-1 indicates a rough grouping of insecticides by their mode of action. Of the five categories listed, metabolic inhibitors and neuroactive agents are the two major groups of modern insecticides.

Anticholinesterases and some of the other nerve poisons are also metabolic inhibitors, but they differ by specifically attacking the nervous system, or atleast their actions on the nervous system constitute the major cause of insect (or mammal) death.

The action of any insecticide could be multiple and that to trace its effect to a primary target is not always possible. The cause of death need not be congruent with the mode of action of an insecticide.

For example, mosquito larvae exposed to an insecticide often die from lack of oxygen because they cannot reach the surface of the water, but the mode of action of the insecticide may be the inhibition of cholinesterase or any other immobilizing effect.

The Nervous System

The majority of the modern insecticides owe their toxicity to their ability to attack the nervous system as the primary target.

The nervous system is one of the most susceptible and vulnerable portions of the body of highly developed organisms.

The striking feature of insects is that they have such a well-developed central nervous system, almost comparable in organization to that of mammals.

Poisoning the nervous system is the quickest and surest way of chemically upsetting the regular body mechanisms.

The central nervous system, as its name implies, serves as the central integration system and is composed of millions of nerve cells which are connected with one another by junctions called synapses.

The peripheral nervous system is composed of two subdivisions:

- The somatic system
- The autonomic system

INSECT NERVOUS SYSTEM

The insect nervous system is considerably simpler than that of mammals. However, in some instances, certain parts of it are highly specialized for adaptation to a complex mode of life.

The basic differences between the insect nervous system and that of mammals are that in insects:

- ❖No cholinergic systems are involved in the peripheral nervous system.
- ❖No distinct autonomic system exists. (There is an autonomic system which is mainly controlled by hormones).

- ❖ No ganglia are involved in the peripheral nervous systems. (The ganglia of insects correspond to the mammalian central nervous system).
- ❖ No chemical transmitter has been identified in the insect central nervous system other than acetylcholine, though it is believed that some active biogenic amines exist.

Besides the gross differences, the insect nervous system has the morphological and histological differences:

1. There is no distinct myelination observable in the insect nervous system.

2. The insect nerve cords are covered with a tough fibrinous sheath, called simply the "nerve sheath," which limits the entry of many substances. The sheath is said to be necessary to protect the nerve cord,

and it seems to serve a similar purpose as the "blood-brain barrier“ of the mammal.

3. The insect neuromuscular junction has no specific "end plates" as in the mammalian junction. The insect axon branches out into several

"twigs" and innervates single muscle fibers, whereas the end plate of the mammalian system governs the whole group of muscle fibers.

4. The insect nervous system is supplied with tracheal systems which provide oxygen directly to the nerve cells through diffusion.

Action of DDT on Nerves and Theories of Its Mode of Action

The primary target of DDT is indeed the nervous system. The characteristic "repetitive discharge" in the nerve impulse patterns has long been noted. In essence, DDT causes the nerve fibers to produce this repetitive discharge in response to a single stimulus.

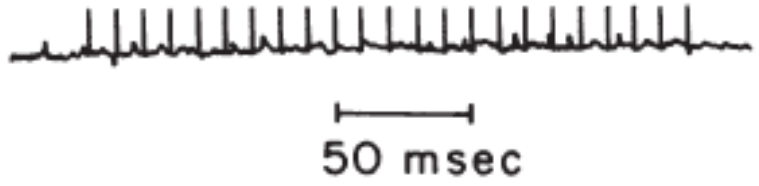

Fig. 4-5. Repetitive discharge caused by DDT treatment of the sensory neuron of *Periplaneta americana*. Redrawn from Yamasaki and Ishii (1954).

Welsh and Gordon pointed out that the phenomenon very closely resembles that of hypocalcemia (caused by reducing the level of calcium and magnesium ions in the perfusing fluid), and they hypothesized that DDT interferes with surface recalcification which is needed to restore a normal resting potential after a single depolarization of the axonic membrane.

In addition to repetitive discharge, DDT-poisoned nerve cords show another characteristic response-"**Prolongation of after potential**". When the negative after potential is increased to a certain level, a sudden burst of repetitive discharges can be provoked by a single stimulus.

According to Narahashi and Yamasaki (1960), the period during which a single stimulus can produce a train of impulses (i.e., repetitive discharge) is relatively short, and finally the nerve reaches a point where it does not elicit multiple discharges. Although there is very little doubt as to the role of negative after potential in the direct process of producing the repetitive discharge in the insect nervous system, involvement of some other factors must be mentioned.

Therefore, it must be considered that DDT alters the axonomic membrane in such a way that the membrane constants (e.g., conductance, resistance, and capacity) themselves become different from those in the normal membrane (N arahashi, 1963 a).

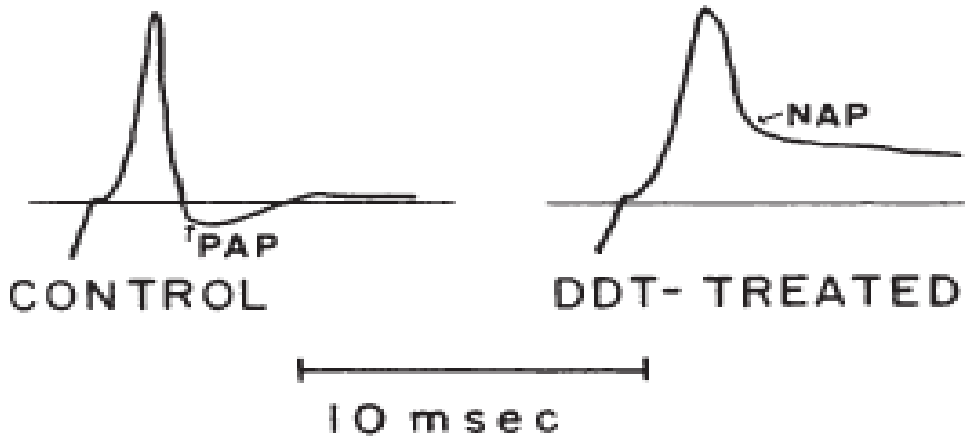

Fig. 4-6. Single action potential recordings of the sensory neuron of *Periplaneta americana* before and after treatment with DDT. PAP, Positive afterpotential; NAP, negative after-potential.

Yamasaki and Narahashi concluded that the permeability of potassium ions across the nerve membranes must be greatly reduced by DDT.

In 1969, it was reported by two groups of researchers (Koch, 1969; Matsumura et ai., 1969; Matsumura and Patil, 1969) that DDT inhibits nerve ATPases. Although Mg-ATPase is affected by DDT, the extent of inhibition appears to be much more significant in (Na + + K+)-ATPase, which plays an important role in the active transport of ions across the nerve membrane.

There are two major problems in attributing this biochemical effect of DDT to its mode of action:

(1) DDT does not cause the same in vivo effects as ouabain, a well-known specific inhibitor of (Na+ + K+)-ATPase

(2) There are many ATPases and systems involving ATP in any given nervous system.

It was found in laboratory (Rashatwar and Matsumura, 1984) that DDT and a number of pyrethroids inhibit the calmodulin stimulated portion of phosphodiesterase activity. Since phosphodiesterase itself was not affected by these chemicals, it has become evident that the above phenomenon represents inactivation of calmodulin's calcium carrying ability.

Calmodulin is known to carry out many important functions by mediating Ca2+ transport to receptors, ion channels, and enzymes (Cheung, 1980). The nervous system in particular has a high titer of calmodulin, indicating the importance of this calcium mediator.

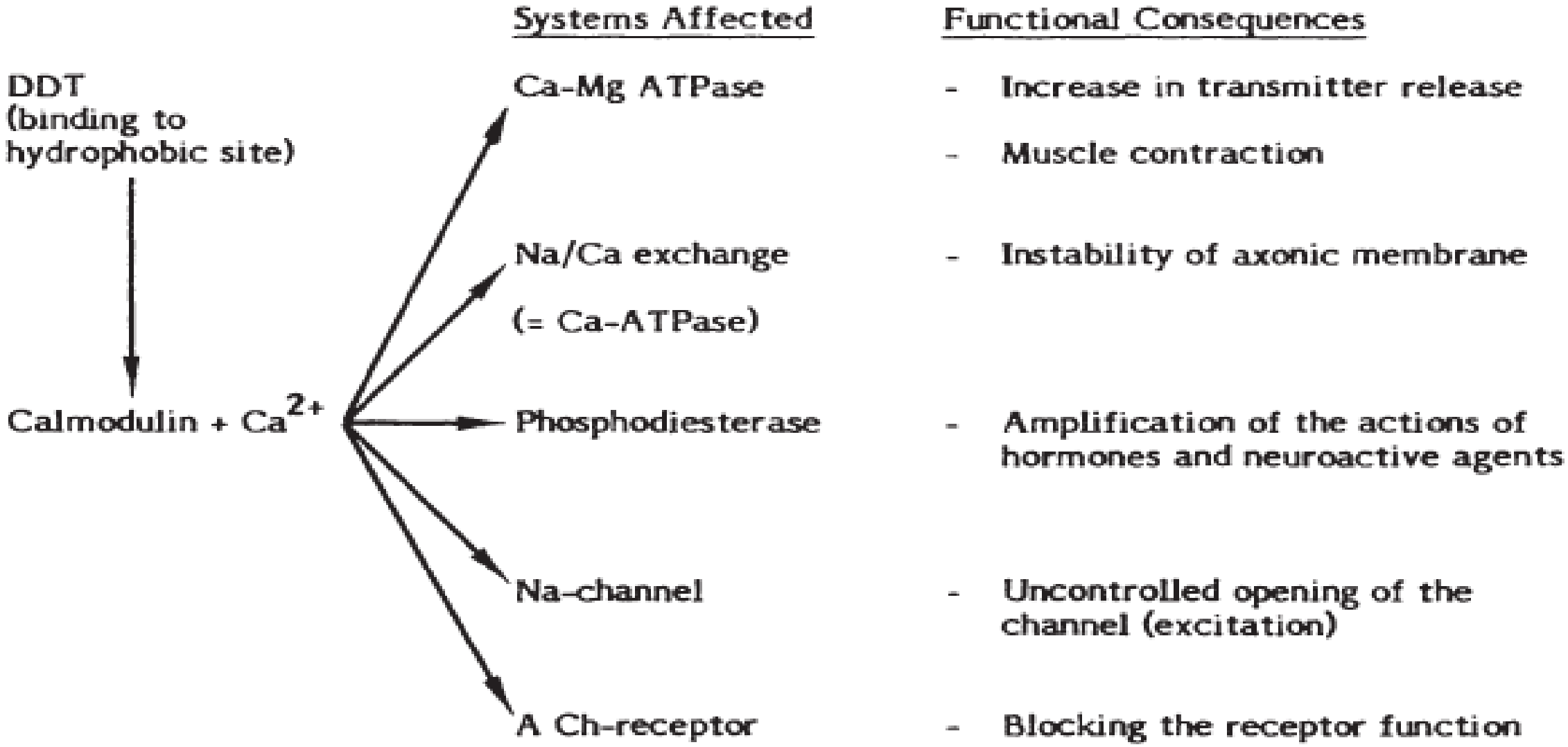

Fig. 4-7. Schematic diagram of potential secondary effects of inhibition of functions of calmodulin by DDT.

References

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