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# Biochemical Processes Related to Insecticide Action: an Overview

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## 1 Introduction

Throughout modern history, man has devised various methods to combat insect pests such as the use of sulfur, chalk, wood ash and plant extracts. Further progress came with the introduction of botanical compounds such as pyrethrum, deris, quassia, and others. The inventory of insecticides used in the 19th century includes sulfur, arsenic, fluorides, soaps, kerosene and various botanicals such as nicotine, rotenone, pyrethrum, sabadilla and quassia (for more details, see Retnakaran et al. 1985; Perry et al. 1998).

During the 20th century, significant progress in the synthesis of new chemicals and standardization of techniques and bioassays has resulted in an evaluation of the structures and biological activity of various compounds. Synthetic insecticides, such as chlorinated hydrocarbons, organophosphates and carbamates, have been developed and used to control insect pests over the past five decades, minimizing losses in agricultural yield and improving human health. Unfortunately, many of these chemicals are harmful to man and beneficial organisms. In some cases they are too persistent in the environment and cause ecological disturbances.

Efforts have been made during the past three decades to develop novel insecticides with selective properties to act on biochemical sites or physiological processes present in a special insect group but differ from others in their properties. This approach has led to the formation of compounds which affect the hormonal regulation of molting and developmental processes in insects such as ecdysone agonists (Wing 1988; Dhadialla et al. 1998), juvenile hormone mimics (Ishaaya and Horowitz 1992, 1995; Ishaaya et al. 1994) and chitin synthesis inhibitors (Cohen 1987; Ishaaya 1990; Oberlander and Silhacek 1998). In addition, compounds which inhibit or enhance the activity of biochemical sites, such as respiration (diafenthiuron) (Ishaaya et al. 1993), or interact with nicotine acetylcholine receptors (imidacloprid, acetamiprid and thiamethoxam) have been introduced for the control of

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aphids and whiteflies (Elbert et al. 1998; Ishaaya and Horowitz 1998). Compounds originating from natural products (abamectin, emamectin, milbemectin and spinosad) and which act on specific biochemical sites, such as GABA and glutamate receptors and chloride channels, have been developed and used successfully to combat agricultural pests (Jansson and Dybas 1998; Bloomquist, this Vol.). *Bacillus thuringiensis*  $\delta$ -endotoxin, which affects the midgut ion exchange, has been developed as an insecticide to control lepidopterans or introduced as a component in transgenic field crops aimed at suppressing important agricultural insect pests (Whalon and McGaughey 1998; Gringorten, this Vol.).

The aim of this report is to present general information on biochemical sites related to insecticide action, while the various chapters of the book discuss up-to-date details and uses of biochemical and physiological sites as targets for developing novel insecticides and of processes relating to resistance mode of action and management.

## 2

### Chitin Synthesis Inhibition

Over the past three decades, two groups of compounds, the benzoylphenyl ureas and buprofezin, have been developed and used as commercial compounds for controlling agricultural pests. Benzoylphenyl ureas act on insects of various orders by inhibiting chitin formation (Ishaaya and Casida 1974; Post et al. 1974) thereby causing abnormal endocuticular deposition and abortive molting (Mulder and Gijswijt 1973). Studies with diflubenzuron [1-(4-chlorophenyl)-3-(2,6-diflubenzoyl)urea], the first commercial compound and the most investigated one in this group, revealed that the compound alters cuticle composition – especially that of chitin – thereby affecting the elasticity and firmness of the endocuticle (Grosscurt 1978; Grosscurt and Anderson 1980). The reduced level of chitin in the cuticle seems to result from inhibition of biochemical processes leading to chitin formation (Post et al. 1974; Hajjar and Casida 1979; Van Eck 1979). Chitin synthetase is not the primary biochemical site for the reduced level of chitin since, in some studies, benzoylphenyl ureas do not inhibit its activity in cell-free systems (Cohen and Casida 1980; Mayer et al. 1981; Cohen 1985). Some of the reports indicate the possibility that benzoylphenyl ureas might: affect the insect hormonal sites, thereby resulting in physiological disturbances such as inhibition of DNA synthesis (Mitlin et al. 1977; DeLoach et al. 1981; Soltani et al. 1984); alter carbohydriase and phenoloxidase activities (Ishaaya and Casida 1974; Ishaaya and Ascher 1977) or suppress microsomal oxidase activity (Van Eck 1979). Recent studies, using imaginal discs and cell-free systems, indicate that benzoylphenyl ureas inhibit 20E-dependent GlcNAc incorporation into chitin (Mikolajczyk et al. 1994; Oberlander and Silhacek 1998). These findings suggest that ben-

zoylphenyl ureas affect ecdysone-dependent biochemical sites which lead to chitin inhibition.

The search for potent acylureas has led to the development of new compounds such as chlorfluazuron (Haga et al. 1982), teflubenzuron (Becher et al. 1983) and hexaflumuron (Sbragia et al. 1983), which are far more potent than diflubenzuron on various agricultural pests (Ishaaya 1990). One of the recent benzoylphenyl ureas, which is in the process of commercialization, is novaluron {Rimon EC-10, 1-[chloro-4-(1,1,2-trifluoromethoxyethoxy)phenyl]-3-(2,6-difluorobenzoyl)urea}. It acts by both ingestion and contact. It is a powerful suppressor of lepidopteran larvae such as *Spodoptera littoralis*, *S. exigua*, *S. frugiperda*, *Helicoverpa armigera* and *Tuta absoluta*, species known to attack cotton, corn and vegetables. It also efficiently controls the whiteflies *Bemisia tabaci* and *Trialeurodes vaporariorum* and the leaf miners *Liriomyza huidobrensis* and *Perileucoptera coffeella*. Our studies indicated that the LC-50 value of Rimon on third-instar *S. littoralis* fed on treated leaves is ~0.1 mg a.i./l. This value resembles that of chlorfluazuron and is tenfold lower than that of teflubenzuron. Novaluron affects larvae of *B. tabaci* to a much greater extent than chlorfluazuron and teflubenzuron. Total larval mortality was obtained at a concentration of 1 mg a.i./l (Ishaaya et al. 1996, 1998). Artificial rain at a rate of 40 mm/h applied 5 and 24 h after treatment in a cotton field had no appreciable effect on the potency of novaluron on *S. littoralis* larvae (unpubl. results). Hence, novaluron can be used in tropical areas and in rainy seasons.

In general, benzoylphenyl ureas have no effect on parasitoids and are considered to have a mild effect on other natural enemies (Ishaaya 1990). As such, they are considered important additions in integrated pest management (IPM) programs.

Buprofezin (Applaud, 2-*tert*-butylimino-3-isopropyl-5-phenyl-1,3,5-thiadiazinan-4-one), a chitin synthesis inhibitor which acts specifically on sucking pests such as plant hoppers and whiteflies, has been developed by Nihon Nohyaku, Japan (Kanno et al. 1981). Its mode of action resembles that of benzoylphenyl ureas, although its structure is not analogous. The compound inhibits incorporation of  $^3\text{H}$ -glucose and N-acetyl-D- $^3\text{H}$ -glucosamine into chitin (Izawa et al. 1985; Uchida et al. 1985). The characteristic symptoms in the greenhouse whitefly *Trialeurodes vaporariorum* resembled those obtained with benzoylphenyl ureas (De Cock and Degheele 1991). As a result of chitin deficiency, the procuticle of the whitefly nymphs loses its elasticity and the insect is unable to molt (De Cock and Degheele 1998). Buprofezin is a powerful suppressor of larval metamorphosis and embryogenesis in the rice plant hopper *Nilaparvata lugens* and in the whiteflies *B. tabaci* and *T. vaporariorum* (Nagata 1986; Yasui et al. 1987; Ishaaya et al. 1988).

The chitin synthesis inhibition site has proved to be important for developing control agents which act selectively on important groups of insect pests.

### 3 Ecdysone and Juvenile Hormone Receptors

Physiological and biochemical processes that govern growth, development, and reproduction in insects are regulated by juvenile and molting hormones. During the past two decades, many investigations have been directed towards elucidating the possible use of ecdysteroids and juvenile hormone (JH) receptors as target sites for developing novel insecticides (Bergamasco and Horn 1980; Horn et al. 1981; Riddiford 1985; Riddiford et al. 1987; Dhadialla et al. 1998). Several substituted dibenzoyl hydrazines which act as ecdysone agonists have been synthesized by Rohm and Haas Co. (Spring House, Pennsylvania, USA). Two compounds, tebufenozide and methoxyfenozide, have been commercialized and used to control lepidopteran pests (Dhadialla et al. 1998; Smagghe and Degheele 1998). These compounds bind to the ecdysteroid receptors thereby initiating the molting process (Wing 1988; Wing et al. 1988; Retnakaran et al. 1995; Palli et al. 1996). Ecdysone agonists are powerful toxicants which act specifically on lepidopteran pests such as *Manduca sexta* (Wing et al. 1988), *Plodia interpunctella* (Silhacek et al. 1990), *Spodoptera frugiperda* (Monthéan and Potter 1992), and *S. littoralis* (Smagghe and Degheele 1992; Ishaaya et al. 1995). The potency of tebufenozide against agricultural pests has been demonstrated against several lepidopteran pests such as the codling moth *Carpocapsa* (*Cydia*) *pomonella* in apple orchards (Heller et al. 1992), the fall armyworm *S. frugiperda* in maize, the bollworm *Heliothis zea* (Chandler et al. 1992) and the armyworms *S. exigua*, *S. littoralis* and *S. exempta* in cotton, cereal, rice and vegetables (Chandler et al. 1992; Smagghe and Degheele 1994; Ishaaya et al. 1995). Methoxyfenozide, a recently developed ecdysone agonist, was five- to tenfold more potent than tebufenozide, and both have no appreciable cross-resistance with conventional insecticides such as pyrethroids and organophosphates (Ishaaya et al. 1995). These compounds are considered highly selective with no harm to parasitoids and predators (Dhadialla et al. 1998; Smagghe and Degheele 1998) and fit well in IPM and insecticide resistance management (IRM) programs.

Among the JH mimics, fenoxycarb and pyriproxyfen exhibit reasonable field stability and high potency on agricultural pests. Fenoxycarb, ethyl [2-(4-phenoxyphenoxy)ethyl] carbamate, was the first commercial compound to be marketed for the control of agricultural pests (Dorn et al. 1981; Masner et al. 1987; Peleg 1988). Pyriproxyfen, 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine, is a fenoxycarb derivative in which a part of the aliphatic chain has been replaced by pyridyl oxyethylene. The compound is a potent JH mimic affecting the hormonal balance in insects resulting thereby in strong suppression of embryogenesis, metamorphosis and adult formation (Itaya 1987; Kawada 1988; Langley 1990; Koehler and Patterson 1991). Pyriproxyfen is considered a leading compound for controlling whiteflies (Ishaaya and Horowitz

1992, 1995; Ishaaya et al. 1994) and scale insects (Peleg 1988), and it is one of the most important components in IRM strategy in cotton fields (Horowitz and Ishaaya 1994; Dennehy and Williams 1997; Horowitz et al. 1999).

Compounds which act on insect hormonal receptors are considered important selective insecticides for controlling insect pests. Extensive research is being undertaken by several chemical companies aimed at synthesizing more potent and selective ecdysone agonists and JH mimics to be used in our agricultural systems.

## 4

### Acetylcholine Receptors

Efforts have been made to develop nicotinyl insecticides with high affinity to insect nicotinic acetylcholine receptors (nAChR), resulting in the development of a new group of neonicotinoid insecticides (Abbink 1991; Tomizawa and Yamamoto 1992; Liu and Casida 1993; Elbert et al. 1998). Neonicotinoids of potential use in agriculture are imidacloprid, acetamiprid and thiamethoxam. These compounds interact with nAChR in a structure-activity relationship (Tomizawa et al. 1995a,b), resulting in excitation and paralysis followed by death. Their selectivity results from a higher affinity to the insect nAChR as compared to that of vertebrates, in contrast to the original nicotine compound (Tomizawa et al. 1995b). Hence it has been suggested that imidacloprid and related compounds be called neonicotinoids (Yamamoto et al. 1995).

Imidacloprid displaced radiolabeled  $\alpha$ -bungarotoxin, a specific ligand of nAChR, in the ganglia of the American cockroach, indicating its direct interaction with the receptor (Elbert et al. 1998). Electrophysiological studies with imidacloprid on the cholinergic motor neuron of *Periplaneta americana* revealed a depolarization of the cell membrane similar to that of acetylcholine (Bai et al. 1991). High affinity of radiolabeled imidacloprid to the binding site was also observed in housefly head membrane (Liu and Casida 1993) and the green peach aphid (Nauen et al. 1996). One of the important features of these compounds is their selectivity towards insects; their affinity to interact with rat nAChR was 1000 times weaker than that with the insect receptor (Methfessel 1992; Zwart et al. 1994).

Imidacloprid, 1-(6-chloro-3-pyridylmethyl)-*N*-nitro-2-imidazolidinimine, and acetamiprid, (*E*)-*N*<sup>1</sup>-[(6-chloro-3-pyridyl)methyl]-*N*<sup>2</sup>-cyano-*N*<sup>1</sup>-methylacetamidine, are the first neonicotinoids to be commercially used to control agricultural pests. They are also called chloronicotinyl insecticides, indicating the biological importance of the *chlorine* moiety in their chemical structure (Leicht 1993). Imidacloprid is a relatively polar material with good xylem mobility suitable for seed treatment and soil application (Elbert et al. 1998). Comparative assays carried out in standardized growth chambers indicate that in soil application imidacloprid gave superior performance for controlling the

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