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MECHANISMS OF SELECTIVE ACTION OF PYRETHROID INSECTICIDES

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INTRODUCTION

History

All four major classes of organic insecticides are neurotoxicants. The chlorinated hydrocarbons such as DDT, lindane, dieldrin, and toxaphene, which act on nerve membranes or synapses, achieved dominance at first but have largely been replaced because of unacceptable persistence and/or types and degrees of chronic toxicity. Organophosphorus (OP) compounds such as parathion, malathion, and diazinon, and methylcarbamate (MC) esters like carbaryl, carbofuran, and aldicarb, which act as acetylcholinesterase (AChE) inhibitors, filled gaps in insect control capabilities and continue even now to increase in importance. The success of the synthetic pyrethroids, the newest major class of insecticides for crop protection, is due to their high potency and selectivity as nerve poisons, which is the subject of this review.

Chemistry

The pyrethrins and the less active jasmolins and cinerins (Figure 1) are six natural insecticidal esters obtained by extracting dried pyrethrum flowers, grown mainly in Kenya, to produce pyrethrum extract. Pyrethrin *I* is the most active ingredient for kill and pyrethrin *II* for rapid insect knockdown. These natural esters, referred to as the "pyrethrins," are characterized as follows: effective at low dose in causing knockdown and kill of a wide variety of household, veterinary, and stored-products insects; low mam-

"pyrethrins" and other rethrins	tetrahydrophthalimidomethyl, benzylfurylmethyl, and phenoxybenzyl esters	cyanophenoxybenzyl esters
pyrethrin I $1A_p$ (1)	tetramethrin 1C (4)	cyphenothrin 1F (8)
pyrethrin II $2A_p$ (1)	resmethrin 1D (1 or 4)	cypermethrin 3F (8)
jasmolin I $1A_j$ (1)	ethanomethrin 7D (1)	deltamethrin 4F (1)
jasmolin II $2A_j$ (1)	kadethrin 8D (1)	tralocythrin 5F (2)
cinerin I $1A_c$ (1)	phenothrin 1E (4)	tralomethrin 6F (2)
cinerin II $2A_c$ (1)	permethrin 3E (4)	ferpropathrin 9F (2)
allethrin 1B (1, 2, 8)		fenvalerate 10F (4)
terallethrin 9B (2)		fluvalinate 11F (4)

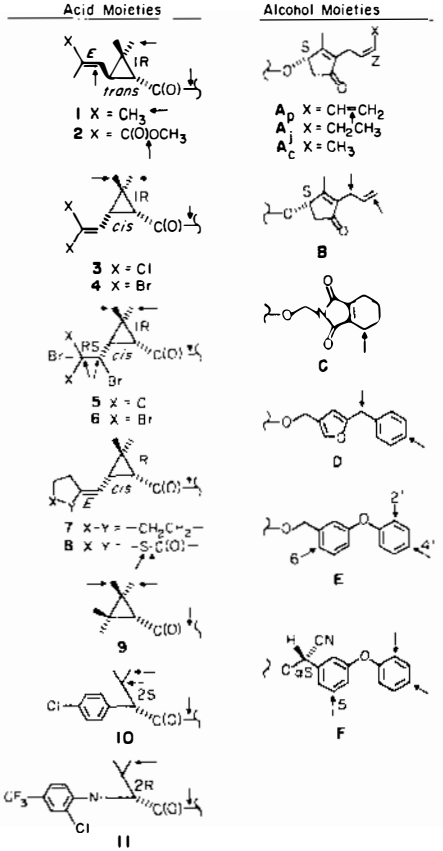

Figure 1 Pyrethroid insecticides derived from various acid (1–11) and alcohol (A–F) moieties shown as the naturally occurring (*1, 2, A*) or most insecticidal isomer. Arrows designate known sites of metabolic attack (references in text). The number of potential isomers is 2^n where n is the total of *R/S, Z/E* and *cis/trans* centers. The numbers of isomers in commercial products are indicated in parentheses. The single isomer product of 1B is S-bioallethrin and of 1D is bioresmethrin.

malian toxicity by all normal routes of exposure; no persistent residues; insufficient stability for use in controlling crop pests; inadequate production to meet current demands (1–6).

Synthetic pyrethroids (Figure 1), structurally optimized over the past half century (6–16), currently include such compounds as allethrin and four other chrysanthemates (tetramethrin, resmethrin, phenothrin, and cyphenothrin). These pyrethroids are used as 1RS,*cis,trans* isomer mixtures or as the 1R,*trans* isomer, which is given the prefix "bio," e.g. bioresmethrin and S-bioallethrin, in the latter case with the insecticidal *S*-alcohol configuration. Allethrin, tetramethrin, and the newer compounds terallethrin and kadethrin are quite useful in their ability to produce knockdown of many flying household and veterinary pests. The most potent knockdown agents have carbonyl groups within the acid (*2* and *8*) or alcohol moieties (*A–C*). The other chrysanthemates, resmethrin, phenothrin, and cyphenothrin, are used against household, veterinary, and stored-products pests but have limited crop use because of their relatively rapid photodegradation and often less than optimal potency. The effectiveness and stability, however, have been substantially increased with the substitution of a dihalovinyl-containing acid moiety (*3* and *4*) (*e.g.* permethrin) and the potency is further enhanced with esters of α-cyanophenoxybenzyl alcohol (*F*) (cypermethrin, deltamethrin, fenvalerate, and fenpropathrin). Some recent pyrethroids, such as fenvalerate, no longer contain the cyclopropane ring, but do retain the overall pyrethroid molecular configuration. Several additional pyrethroids are entering small scale commercial use and are in general close analogs of the compounds considered above.

The antipodes of the pyrethroids illustrated in Figure 1 are essentially inactive compared with their "biomimetic" isomers. The most active isomer of cypermethrin (the 1R,*cis,* αS isomer equivalent in configuration to deltamethrin) is only 10–15% of the commercial product, and the remaining isomers, with the exception of 1R,*trans,* αS, are essentially impurities. Current pyrethroids can easily be rationalized as evolving from a sequence of isosteric changes in the structure of pyrethrin *I,* but the critical features for pyrethroid-like activity are becoming increasingly difficult to define. The configuration of the entire molecule appears to be more important than any structural requirements for specific functional groups. It is in fact possible to maintain moderate insecticidal activity with compounds possessing acid or alcohol moieties lacking any cyclic substituent or chiral center and with amide, ketone or oxime ether (Figure 2) replacements for the ester group.

The natural pyrethrins and early synthetic chrysanthemates (esters with acid moieties 1 and 2) are generally more active as contact than as stomach poisons, but the newer, more stable compounds are now very potent on ingestion as well. Residual activity is important for maximum effectiveness,

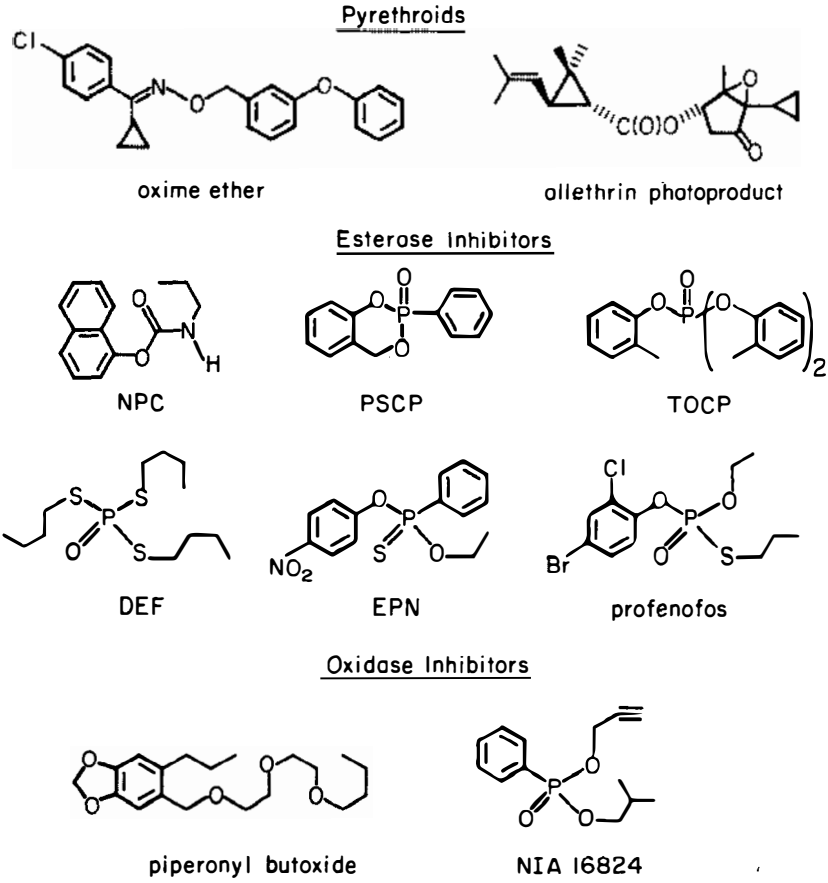

Figure 2 Pyrethroids and synergists discussed.

and permethrin, cypermethrin, deltamethrin, and fenvalerate often provide control for several weeks following a single application. This increased stability means that care must be taken in evaluating residues persisting on crops. The newer pyrethroids are also less susceptible to metabolic attack in insects and in some cases in mammals; thus it is important to consider their metabolic fate.

Selective Action

Pyrethroids more than any other major class of insecticides provide favorable selectivity for insects compared with mammals. The "pyrethrins" were once labeled as "nontoxic to humans and pets" and are generally considered to be the safest or among the safest of the highly potent insecticides. Selec-

tivity ratios for rat oral LD_{50}/insect topical LD_{50} (mg/kg) average as follows for different types of insecticides: MCs-16, OPs-33, chlorinated hydrocarbons-91, and pyrethroids-4500 (11). These broad generalizations should be viewed with caution and actual selectivity ratios analyzed on the basis of individual compounds and systems.

Table 1 illustrates several aspects of the selective toxicity. Pyrethroids generally have a broad spectrum of activity and high potency when applied topically to insects. They have a low oral and intraperitoneal toxicity to mammals even though some pyrethroids have a high intrinsic mammalian toxicity, i.e. intravenous and intracerebral routes of administration. The *cis* isomers are generally more toxic than the corresponding *trans* isomers. The *trans* isomers of resmethrin, phenothrin, and permethrin have very low mammalian toxicity despite their similar insecticidal potencies to their *cis* isomers. Introduction of the α-cyano group, e.g. permethrin vs cypermethrin, increases both the insect and mammalian toxicity. Cockroach cercal sensory nerves are highly sensitive to repetitive firing caused by compounds without an α-cyano group (Type I action) but not with an α-cyano group (Type II action). The rate of metabolic detoxification is dependent on such structural features as the *cis* or *trans* configuration of the acid moiety and the presence or absence of the cyano substituent in the alcohol moiety.

Seemingly small structural changes sometimes have a large influence on the relative potency and species selectivity of pyrethroids. Lacewing larvae are highly tolerant to pyrethroids, especially deltamethrin, which for other insects is usually the most potent toxicant (26). Larvae of the noctuid, *Plutella xylostella,* resistant to deltamethrin and many closely related compounds, are highly sensitive to the 1R,*trans* isomer of *4D* (Figure 1), a compound that is usually a relatively poor insecticide (27). Pyrethroids are very toxic to honeybees, but the structural modifications for optimal potency to flies substantially differ from those to honeybees (23). Mites survive insecticidal doses of most pyrethroids but are very sensitive to fenpropathrin and to analogs of fenvalerate and fluvalinate with a 4-*t*-butyl group in place of the 4-chloro substituent (28, 29).

Several insect species resistant to DDT are cross-resistant to pyrethroids (23, 30). Field and laboratory selection of houseflies and mosquito larvae with pyrethroids may give highly resistant strains approaching almost total immunity. High levels of resistance have also been noted for several species of noctuid larvae and for aphids and cattle ticks. Despite precautions to minimize the spread of resistance, its development may eventually make it uneconomical to use pyrethroids in some control situations for which they are currently very effective.

Pyrethroids are generally considered to be an improvement over other insecticides relative to their environmental impact when applied at insecti-

Table 1 Pyrethroid structure-activity and structure-biodegradibility relationships

Pyrethroid	Type of action[a]	Approximate LD_{50}, mg/kg							Nerve potency, M[d]	Detoxification rate, mouse liver[e]	
		Insect topical[b]			Mammal[c]						
					Rat		Mouse				
		Hf	Mb	Ac	Oral	iv	ip	ic		Esterase	Oxidase
Pyrethrin *I*[f]	I	15	1.1	1.2	900			> 35	4×10^{-9}	< 3	42
Allethrin	I	3	40	0.5	680		30	4	2×10^{-9}	< 2	44
Tetramethrin	I	5	40	57	> 5,000			> 12	3×10^{-13}	25	62
Kadethrin	I	0.8	3	1.2	600			1.2	6×10^{-10}	< 3	51
Resmethrin											
1R,*trans*	I	0.3	1.6	1.0	8,000	340	> 1,500	> 120	$\leq 10^{-9}$	80	20
1R,*cis*	I	0.7	3	0.3	100	7	320	0.6	8×10^{-10}	< 3	29
Phenothrin											
1R,*trans*	I	0.6	3.6	0.7	10,000	> 300	> 1,500	> 120	8×10^{-9}	59	27
1R,*cis*	I	0.7	10	0.7			> 1,500	> 60	9×10^{-9}	< 4	37

Permethrin											
1R,*trans*	I	0.3	0.3	0.6	2,000	>270	>500	>12	8×10^{-9}	77	30
							500				
1R,*cis*	I	0.1	0.5	0.09		>135		0.2	7×10^{-9}	<2	26
Fenpropathrin	I/II	0.5	2.0	0.02	25	1			1×10^{-9}	10	13
Cypermethrin											
1R,*trans*,αS	II	0.02	0.07	0.01	500	45	>125	0.02	$>10^{-6}$	17	4
1R,*cis*,αS	II	0.01	0.03	0.02		2	7	0.008	$>10^{-6}$	<2	5
Deltamethrin	II	0.01	0.03	0.01	100	2	10	0.02	$>10^{-6}$	<3	<4
Fenvalerate	II	0.2	0.4	0.1	450	20	>125	0.01	$>10^{-6}$	<2	11

[a] Based on symptoms in mammals (17–19) and on initiation of repetitive firing in American cockroach cercal sensory nerve in vivo (except kadethrin) and in vitro (19, 20).

[b] Data for adult houseflies (Hf), mustard beetles (Mb), and American cockraoches (Ac) [(8, 20–22) and supplemental findings from this laboratory]. Data for the most insecticidal isomer except [1R,*cis,trans*]-tetramethrin for Mb.

[c] Sources for data are: rat oral [(8, 23), or this laboratory] and intravenous (iv) (17); mouse intraperitoneal (ip) (24) and intracerebral (ic) (18). Data for most insecticidal isomer except for rat oral in which case isomer mixtures for tetramethrin, phenothrin, permethrin, cypermethrin, fenpropathrin, and fenvalerate.

[d] Concentration to initiate repetitive firing in American cockroach cercal sensory nerve (20 or additional studies in this laboratory). Data for most insecticidal isomer.

[e] Relative to overall (esterase + oxidase) metabolism of [1R,*trans*]-resmethrin by mouse liver microsomes (25). Data for most insecticidal isomer except 1RS,αRS for cypermethrin isomers, αRS for fenpropathrin, and 2RS for fenvalerate.

[f] Data based on pyrethrins for Ac, rat, mouse, and nerve potency and pyrethrin *I* in the other cases.

cidal doses. They are, however, very toxic to shrimp, lobster, and fish, as are DDT and some other chlorinated hydrocarbons. Pyrethroids have been less damaging to fish populations than originally anticipated, presumably because of rapid adsorption on particulate materials in a form unavailable to the fish. Frogs are also quite sensitive to pyrethroids (L. M. Cole and J. E. Casida, unpublished observations). On the other hand, pyrethroids have a very low acute toxicity to birds (23, 31).

MODE OF ACTION

Symptomology

Pyrethroids fall into two classes based on the symptoms produced by acutely-toxic doses in poisoned animals, i.e. cockroaches (19, 20), rats (17, 32), mice (18, 19), and frogs (L. M. Cole and J. E. Casida, unpublished observations). The Type I poisoning syndrome, produced by pyrethroids without an α-cyano substituent, is characterized by restlessness, incoordination, prostration, and paralysis in the cockroach (20, 33), and by aggressive sparring, elevated startle response, whole body tremor, and prostration in the rat (also referred to as tremor or T syndrome) (17). A few compounds, e.g. 1R,*trans* isomers of resmethrin, phenothrin, and permethrin produce few or no symptoms, even at extremely high doses, in rats and mice (17, 18, 24), which suggests a possible insensitivity of mammalian nerves to some pyrethroids that have a Type I action in susceptible organisms. Type II symptoms are produced by compounds with an α-cyano substituent. In cockroaches Type II symptoms include incoordination, convulsions, and intense hyperactivity (19, 20), whereas rats display burrowing behavior, coarse tremors, clonic seizures, sinuous writhing, and profuse salivation without lacrimation (also referred to as choreoathetosis/salivation or CS syndrome) (17). Fenpropathrin, an α-cyanophenoxybenzyl pyrethroid, seems to have a mixture of Types I and II effects. It causes predominantly Type I symptoms in the rat (17) but produces primarily Type II with a minor component of Type I symptoms when administered ic to mice (18) and when applied topically to cockroaches (20).

There is increasing evidence that the Type II syndrome involves primarily an action in the central nervous system of mammals, whereas the Type I syndrome may also have peripheral components. This hypothesis was first suggested solely on the basis of symptomology (32). It was subsequently shown that the toxicity of deltamethrin (Type II action) in mice is a function of the amount of parent compound in the brain regardless of the route of administration or previous exposure to metabolic inhibitors, and that this brain level is equivalent to the ic LD_{50} dose (34). On the other hand, the brain concentration of [1R,*cis*]-resmethrin (Type I action) in rats at the time

of death is only about one tenth of that required for an ic LD_{50} in mice (18, 35), and yet mice are usually more sensitive to pyrethroids than rats (23). Compounds causing the Type II syndrome have greater potency when injected into the brain, relative to ip injection, than those with Type I action (18). It should be noted, however, that all active pyrethroids examined are more toxic ic than ip, which indicates that both syndromes can originate in the brain and that compounds producing the Type II syndrome may act exclusively at a site localized in the CNS.

Neurophysiology

NERVE MEMBRANE Nerve excitation by pyrethroids has been examined with giant axons of the cockroach, crayfish, and squid (36, 37). Allethrin causes an increased negative after-potential and repetitive firing following electrical stimulation of cockroach preparations, but only above 26°C (38, 39); nerve blockage occurs at lower temperatures (40), as the toxicity of pyrethroids increases. Voltage clamp studies using squid giant axons showed that allethrin shifts the sodium activation curve in the direction of depolarization (41) and the sodium inactivation curve in the direction of hyperpolarization (40). One or both of these effects could account for the prolongation of the transient sodium conductance increase and are probably also the major reason(s) for repetitive firing and nerve blockage. Another approach has shown that allethrin, permethrin, or DDT applied to voltage-clamped frog myelinated nerve fibers results in a delay in the closing of the activation (m) gate, which causes an increased and prolonged sodium tail current (42, 43). Tetramethrin applied to voltage-clamped squid giant axons also increases the amplitude and duration of the sodium tail current; the falling phase of the transient sodium current (inactivation or h gate) was prolonged without affecting the rising phase (44). It is therefore uncertain whether pyrethroids primarily affect the h or m gate to cause the prolonged inward sodium current in nerve axons. However, it is possible that the findings reflect differences between invertebrate/vertebrate or un-myelinated/myelinated nerve axons. Calcium channels, in those axons where calcium instead of sodium is the inward current carrier, may respond to pyrethroids in a similar way to sodium channels (45).

Nerve blockage by pyrethroids, caused by suppression of the transient sodium conductance increase, is only observed at higher doses than those needed to cause repetitive firing; however, nerve blockage is enhanced at lower temperatures (40, 41, 46). Nerve membrane depolarization has not been associated with the action of noncyano pyrethroids in either cockroach (38) or crayfish (47) giant axons, even at the time of nerve blockage. However, S-bioallethrin gives depolarizing waves with spike bursts in leech

Retzius cells (48), and permethrin results in depolarization of crayfish stretch receptor cell bodies, causing a train of action potentials in the afferent axon (49). In addition, pyrethroids specifically possessing an α-cyano substituent cause a depolarizing block of crayfish giant axons without repetitive firing (50), and deltamethrin blocks the leg nerves of the crab without repetitive discharges (51). There is also evidence for a depolarizing effect of cyano-substituted compounds at segmental motor terminals of housefly larvae, leading to an increased frequency of miniature excitatory postsynaptic potentials (52).

INSECTS AND RESISTANCE Several in vivo and in vitro systems have been used to examine pyrethroid mode of action in insects. Extracellular recordings have been made from dorsal longitudinal flight muscles in pyrethroid-poisoned adult, tethered houseflies (53–55). The muscle fibers are arranged in 6 pairs, each pair innervated by one neuron. In controls, signals from each fiber in one pair occur in synchrony, i.e. are coupled. It is proposed that insecticides that act on the CNS cause "uncoupling" of flight motor potentials whereas peripherally acting ones do not. The possibility that a given insecticide may act both centrally and peripherally is not directly evaluated as CNS recordings are not involved. Caution is also necessary in considering temperature effects in assigning a "peripheral" or "central" label to an insecticide (55), as demonstrated below.

The validity of giant axons as models for elucidating pyrethroid action was challenged on the basis of studies with cockroaches given an LD_{95} dose of pyrethrin *I;* as an alternative, "ganglionic destabilization" was proposed as the critical lesion (56). Unfortunately, no recordings were made from peripheral nerves, or even from single axons in the CNS, and the temperature used (20°C) was below the critical one (26°C) above which cockroach giant axons fire repetitively when dosed with allethrin (38, 39). Indeed, in the cockroach, temperature plays a key role in defining the sites of action of allethrin (33, 57, 58). At 32°C, repetitive firing in the electrode-implanted, free-walking cockroach is observed in the CNS and also in sensory and motor axons after an LD_{95} dose. At 15°C, where allethrin is almost ten times as toxic, repetitive firing is observed in sensory and motor axons instead of rapid nerve blockage as expected from previous in vitro studies (40, 41). Discharges in the CNS at 15°C are secondary; i.e. unlike repetitive firing in sensory axons and in the CNS at 32°C, they can be reproduced by applying physical stress to unpoisoned cockroaches. This qualitative difference provided the first in vivo evidence that the sites and mode of action of an insecticide could vary with temperature.

Pyrethroid-induced discharges in cockroach cercal sensory nerves are less sensitive to temperature variations than those in the CNS, thereby

providing a suitable preparation for mode of action studies (58). A variety of insecticidal pyrethroids lacking the cyano group cause repetitive firing in this sensory nerve in vivo, whereas cyanophenoxybenzyl pyrethroids, except fenpropathrin, do not (20). The activity of compounds producing the Type I syndrome was quantified based on repetitive firing following electrical stimulation in a cercal sensory nerve in vitro (20). The most potent pyrethroids in this assay are, interestingly, the best knockdown agents, e.g. tetramethrin and kadethrin, suggesting that knockdown may be associated with repetitive firing in sensory and/or other peripheral neurons (20, 31). The cockroach cercal sensory nerve assay reveals that the *cis* and *trans* isomers are of similar potency with tetramethrin, phenothrin, resmethrin, and permethrin, whereas the non-insecticidal enantiomers of phenothrin and permethrin have negligible activity (20). These findings are in contrast to studies with isolated crayfish nerve cords (59–62) showing unanticipated stereospecificity (63). Compounds causing Type II effects block the cockroach cercal sensory nerves without repetitive firing or increased activity, but when applied to the cockroach in vivo they cause long trains of motor potentials in the cerci (19, 20). A variety of other insect neurophysiological systems have also been used for pyrethroid structure-activity studies (e.g. 64–67).

Resistance or cross-resistance in insects is, in many cases, associated with decreased nerve sensitivity (23, 30). Housefly resistance to pyrethroids resulting from selection with DDT (68) or pyrethroids (69) that is not overcome by inhibitors of metabolism (see section on detoxification below) is referred to as knockdown resistance (*kdr*). It extends to pyrethroids with both Types I and II actions (70). This type of resistance in houseflies is correlated with decreased nerve sensitivity (repetitive firing) to DDT (71) and pyrethroids in both larvae (72) and adults from European (73) and American colonies (74). The nerve insensitivity in *kdr* flies of 10^3- to $>$ 10^4-fold involves both peripheral nerves (72) and the CNS (73). A neural basis for pyrethroid resistance has also been demonstrated in *Anopheles* mosquitos (75). In addition, reduced sensitivity of the CNS correlates with resistance to permethrin but not cypermethrin in a noctuid larva, the cotton leafworm, at high but not low temperatures (76, 77). The lack of tolerance to cypermethrin in this particular resistant strain was associated with a qualitative difference in its mode of action, providing the first evidence in an insect for two modes of action for pyrethroids: unlike permethrin, cypermethrin did not cause repetitive firing in the abdominal nerve cord (76, 77).

VERTEBRATES AND OTHER NERVE SYSTEMS Extensive studies on the clawed frog have shown that allethrin, permethrin, and DDT cause repetitive firing in various peripheral nerves, with small diameter sensory or

motor nerve endings being the most sensitive (78). Allethrin shows a negative temperature coefficient for repetitive firing in lateral line afferents of the clawed frog, thought to be due to an action at the sense organ (79). In contrast to the above compounds, deltamethrin does not cause repetitive firing in a variety of nerves, but does so in the lateral line afferent axon, where this action is attributed to alterations in sodium conductance parameters (80). This apparent Type I effect may be due instead to an action at the synapse between the lateral line sense organ and the afferent fiber, for which the transmitter is either glutamate or GABA (20).

Mammalian studies thus far have provided little fundamental information on pyrethroid action owing to the inherent complexity of the nerve networks examined. Deltamethrin in the rat causes EEG discharges that appear to be subcortical in origin and are probably mediated via the basal ganglia (81) involving extrapyramidal cells (82). Resmethrin in the rabbit produces abnormal discharges in a variety of nerve fibers, with no single, clearly defined site of action (83), which perhaps suggests an axonal effect as noted above in invertebrates.

Some pyrethroids (i.e. deltamethrin and kadethrin but not resmethrin and permethrin) stimulate ^{22}sodium influx into tissue cultured mouse neuroblastoma cells, but only when used with agents specific to sodium channels and which, by themselves, cause ^{22}sodium influx, e.g. batrachotoxin, veratridine, and sea anemone toxin II (84). There is no negative temperature coefficient in the action of the toxicant combined with pyrethroids from 5° to 37°C. Separate receptors appear to bind pyrethroids and tetrodotoxin, an observation consistent with neurophysiological studies on the squid giant axon (41). Deltamethrin causes slow ($\sim$ 5 sec), depolarizing waves of up to 30 mV in inexcitable tissue cultured C9 nerve cells from rat brain (84). However, some pyrethroids considered to have a Type I action in other systems antagonized the increased sodium influx caused by treatment with veratridine and kadethrin; they also antagonized electrophysiological responses caused by the "active" pyrethroid (i.e. deltamethrin and kadethrin) on neuroblastoma cells (84). It seems possible that both these assays are selective for pyrethroids possessing Type II activity, such as deltamethrin; kadethrin action includes some Type II features in the cockroach (20) and causes profuse salivation, a symptom more commonly associated with cyanophenoxybenzyl compounds, in ic-treated mice (18).

Early biochemical studies on the pyrethrins dealt with disruptions of a variety of enzymes and pathways of intermediary metabolism (85). Pyrethrins and pyrethroids inhibit various adenosine triphosphatases including neural calcium-ATPase and calcium-magnesium-ATPase (86). Allethrin or bioresmethrin poisoning of the hemipteran *Rhodnius* triggers release of diuretic hormone from the CNS into the hemolymph at the paralytic stage

of poisoning, resulting in cyclic AMP-mediated diuresis (87). The first biochemical change observed following treatment of rats with [1R,*cis*]-resmethrin, cypermethrin, and deltamethrin is an increase in cerebellar cyclic GMP (but not cyclic AMP) which occurs, at least with cypermethrin, before the onset of convulsions (88, 89). There are also localized changes in brain glucose utilization on dosing rats with deltamethrin, most notably in the cortex and hippocampus, but not in the cerebellum (90).

Various radioactive ligands have been used in an attempt to localize binding sites relevant to pyrethroid action. Many studies employed [^{3}H]- or [^{14}C]-pyrethroids, e.g. tetramethrin binds preferentially to the fraction of rat brain containing myelin sheath materials (91). Deltamethrin partially inhibits [^{3}H]-kainic acid, a glutamate analog, from binding to mouse forebrain membranes (92). [^{3}H]-Dihydropicrotoxinin binding in rat brain membranes is inhibited by deltamethrin but not by its nontoxic αR isomer (93). [^{35}S]-4-*t*-Butyl-1-phospha-2,6,7-trioxabicyclo [2.2.2] octane-1-sulfide, a potent and selective noncompetitive GABA antagonist, appears to be particularly useful in studies of pyrethroid action in rat brain membranes as, in studies with 35 pyrethroids, the specific binding of the radioactive ligand is inhibited by all cyanophenoxybenzyl pyrethroids that cause the Type II syndrome, but not by their nontoxic stereoisomers or by any pyrethroid producing the Type I syndrome. Furthermore, the inhibitory potency of pyrethroids in this binding assay correlates directly with their intracerebral toxicity in mice (L. J. Lawrence and J. E. Casida, unpublished observations). The latter finding is of special interest because of its stereospecificity; when combined with the protective effect of diazepam for deltamethrin and fenvalerate poisoning described below it strongly suggests that the GABA receptor/ionophore complex is the primary site of Type II pyrethroid action. Electrophysiological evidence for the involvement of this complex in the Type II syndrome comes from conductance measurements in crayfish claw opener muscles. Here, 4 pyrethroids with Type II action caused an increase in input resistance in fibers exposed to GABA whereas 2 nontoxic stereoisomers and 3 pyrethroids causing the Type I syndrome did not (D. W. Gammon and J. E. Casida, unpublished observations).

Antidotes

The excellent safety record of pyrethroids is partially responsible for the limited effort invested in the search for effective antidotes. Atropine blocks salivation in rats poisoned with cypermethrin but does not prevent the dramatic increase in cyclic GMP levels in the cerebellum (89). In addition, it also blocks salivation in mice treated ic with cypermethrin without altering the LD_{50} (18). The centrally acting drug mephenesin protects rats from deltamethrin and [1R,*cis*]-resmethrin toxicity, but only when administered

at doses that cause profound muscle relaxation (20–35 mg/kg, iv) (94). Pretreatment with low doses (0.3–1 mg/kg, ip) of diazepam delays the onset of symptoms in mice following ic administration of pyrethroids causing the Type II but not the Type I syndrome (19), further indicating two different modes of action for pyrethroids. A higher dose (3 mg/kg) of diazepam increases the ic LD_{50} values in mice by 6- to 9-fold for deltamethrin and permethrin (19). It has also been reported that diazepam (10 mg/kg), aminoxyacetic acid (50 mg/kg), and cycloheximide (1 mg/kg) injected ip protect against the neurotoxic symptoms of permethrin in mice (95).

Relation to Selective Toxicity

It is very likely that there are marked species and strain differences in the configuration or sensitivity of the relevant target sites that interact with pyrethroids. The mammalian nervous system, in contrast to insect nerves, appears to be insensitive to the 1R,*trans* isomers of resmethrin, phenothrin, and perhaps permethrin. Surprisingly, mammals as well as insects are very sensitive to the closely related [1R,*trans*]-ethanomethrin, which also has a Type I action (24). Other structural alterations (e.g. an α-cyano substituent) may change not only the selectivity but also the type and site of pyrethroid action. Resistant insects with the *kdr* factor probably have modified pyrethroid target sites.

PHARMACOKINETICS AND METABOLIC FATE

Distribution and Localization

Pyrethroids are lipophilic molecules that generally undergo rapid absorption and distribution following ingestion by birds and mammals. Unless isolated in lipid depots they are quickly metabolized and eliminated from the body. Thus, permethrin persists longer in fat than in other tissues of chickens (96), rats (97), goats (98), and cows (99). *cis*-Permethrin is retained longer than its more metabolically-labile *trans* isomer in the fat of mammals, the milk of cows and goats, and the fat and eggs of chickens (96-100); this same isomer specificity applies to cypermethrin in the fat of rats and mice (100–102). Sometimes a portion of an oral pyrethroid dose appears unmetabolized in feces, e.g. pyrethrins *I* and *II* in rats (103) and permethrin in Rhesus monkeys (104), suggesting biliary excretion or lack of absorption. Enterohepatic circulation is involved in the elimination of tetramethrin and resmethrin metabolites from treated rats (105, 106). In rainbow trout the permethrin isomers are readily eliminated, though they are persistent in fat, and the metabolites are excreted in the most part via the bile (107). In carp [2S,αRS]-fenvalerate is much more rapidly metabolized and eliminated than DDT (108). The enantiomeric pyrethroids generally have the same pharmacokinetic behavior, i.e. the 1R and 1S isomers

follow similar patterns of distribution and persistence as examined with *cis*- and *trans*-permethrin in rats (97) and *cis*-4E in American cockroaches (109).

Some pyrethroid metabolites persist in mammals long after the parent compound is metabolized and eliminated. A fragment from the alcohol moiety of resmethrin, possibly 5-benzyl-3-furancarboxaldehyde, undergoes slow elimination apparently associated with binding to liver components (110, 111). Cyanide liberated on metabolism of deltamethrin, cypermethrin, and fenvalerate in rats is incorporated into skin and stomach components, probably as thiocyanate, which may form mixed disulfides with tissue proteins (101, 112, 113).

Detoxification

The metabolic fate of pyrethrins and pyrethroids has been recently reviewed on a general basis (16, 114) and with special emphasis on mammals (115) and insects (116).

SITES OF ATTACK AND PATHWAYS All pyrethroids are metabolized by ester hydrolysis and oxidation at methyl, methylene, alkenyl, or aryl substituents (Figure 1). The metabolites are generally excreted by insects, birds, and mammals as alcohols, phenols, or carboxylic acids and their glycine, sulfate, glucuronide, or glucoside conjugates. At least 80 metabolites are identified from *cis*- and *trans*-permethrin alone in various species and systerms. Some of the more notable metabolites of permethrin are: 4'-hydroxypermethrin and permethrin hydroxylated at the *cis*- and/or *trans*-methyl group in housefly adults, cabbage looper larvae, rainbow trout, chickens, rats, goats, and cows (96–99, 107, 117); 2'-hydroxypermethrin in rats (96); 6-hydroxypermethrin in houseflies (117); conjugates of the acid moiety or of 3-phenoxybenzoic acid with glycine, serine, glutamic acid, and glutamine in insects (117), with glutamic acid in the cow and goat (98, 99), with taurine in the mouse (118), and with glycyl-valine in the mallard duck (119); 2- and 3-(3-phenoxybenzoyl)dipalmitins in the skin of rats (120); esters oxidized at two distinct sites (97, 99); sulfate conjugates of the hydroxylated esters (96). The acid moiety of fluvalinate is conjugated with cholic, taurochenodeoxycholic, and taurocholic acids in the cow, chicken, and rat, respectively (121). Metabolism of chrysanthemates is dominated by reactions at the isobutenyl group, i.e. oxidation of the methyl substituent *trans* to the cyclopropane (103, 110, 111, 122, 123) or epoxidation with subsequent hydrolysis of the epoxychrysanthemate and a nonenzymatic concerted decarboxylation and oxirane-opening (122).

The in vivo persistence and sometimes the sites of metabolism are greatly affected by treating houseflies and milkweed bugs with piperonyl butoxide

(123, 124), milkweed bugs with NPC, DEF, and NIA 16824 (124), and rats with piperonyl butoxide, DEF, TOCP, PSCP, and profenofos (100) (Figure 2). Thus, multiple pathways are normally used in pyrethroid metabolism and block of one pathway shifts the metabolic attack to other sites.

Most pyrethroid metabolism results in detoxification, but there are exceptions. Tetramethrin undergoes slow Michael addition with glutathione under physiological conditions and the conjugate readily reverts to the parent compound; the significance of this reaction in vivo is not clearly established (106). Epoxychrysanthemates are formed metabolically (122) and retain moderate insecticidal activity. [1R,*trans*]-Resmethrin, though possessing low mammalian toxicity, produces poisoning symptoms following a lethal iv dose in rats only after an appreciable delay, suggesting that a metabolite may be more toxic than the parent compound (125), *e.g.* [1R,*trans*]-chrysanthemic acid (110). The tetrahaloethyl pyrethroids tralomethrin and tralocythrin (5F and 6F) undergo nonenzymatic debromination in rats and insects, yielding the dihalovinyl pyrethroids deltamethrin and cypermethrin respectively (126, 127).

ESTERASES AND THEIR INHIBITORS As shown in Table 1, mouse liver microsomal esterases hydrolyze the *trans*-cyclopropanecarboxylates of primary alcohols (i.e. tetramethrin, resmethrin, phenothrin, and permethrin) very rapidly compared with the corresponding *cis*-isomers (resmethrin, phenothrin, and permethrin). Pyrethrin *I* and allethrin, derived from secondary alcohols, are poorly hydrolyzed, as is the *cis*-cyclopropanecarboxylate kadethrin. The α-cyano group reduces the hydrolysis rate of phenoxybenzyl esters (i.e. cypermethrin and deltamethrin vs permethrin), but fenpropathrin and fenvalerate are still hydrolyzed at appreciable rates. The R and S isomers of esters derived from 1, *trans*-3, and 10 are hydrolyzed at somewhat different rates (25). These structure-biodegradability findings from esterase studies are relevant in vivo to rats and mice since the majority of excreted pyrethroid metabolites are products of ester hydrolysis, except for those derived from the rethrins (1A and 1B) and the *cis*-cyclopropanecarboxylates. Lacewing larvae are an interesting exception to this rule; their esterases hydrolyze cyano-pyrethroids and *cis*-isomers faster than a non-cyano, *trans* isomer such as *trans*-permethrin (26).

Most in vitro studies have utilized mouse or rat liver microsomes as the pyrethroid esterase source, as the microsomes are much more active than other homogenate fractions (128–130). Significant activity is also found in mouse plasma and kidney microsomes (130) and many other mammalian and insect tissues (113). A rat liver microsomal pyrethroid esterase has been partially purified and its properties are similar to malathion carboxyesterase (129). However, selective inhibition studies establish that hydrolysis of

malathion, *trans*-permethrin, and *cis*-permethrin by rat and mouse liver microsomal preparations involves several esterases with differing substrate specificities (131). Permethrin isomers are cleaved more slowly by fish liver than by mouse liver microsomes but with the same *cis/trans* specificity (130). The substrate specificity varies somewhat among different insect preparations (26, 132–135) and esterases significant in detoxification appear in both the gut and integument of lepidopterous larvae (133–135).

Esterase inhibitors are of interest in evaluating the significance of esterases in detoxification and as synergists for increasing pyrethroid toxicity to insects. They may also create unanticipated hazards by enhancing pyrethroid toxicity to mammals. Commonly used inhibitors are shown in Figure 2. Some synergism factors using various esterase inhibitors in different species are: 35X for NPC with *trans*-tetramethrin in milkweed bugs (124); 68X for PSCP with *trans*-permethrin in lacewing larvae (26); > 40X for DEF, EPN and profenofos with fenvalerate in mice (136); > 188X for DEF with [1R,*trans*]-ethanomethrin in mice (24); 20X for profenofos with *cis*-cypermethrin in cabbage looper larvae (133). The OP insecticide ethion increases the toxicity of deltamethrin to a DDT-resistant strain of cattle tick (27, 137). Pyrethroids are used in many areas in which the pests are also exposed to OP and MC insecticides, and synergism is undoubtedly involved in some of these uses. Optimization of pyrethroid synergists has proved complicated because the degree of potentiation of toxicity varies with the pyrethroid and species under consideration.

OXIDASES AND THEIR INHIBITORS The microsomal mixed-function oxidase (MFO) system is involved in the detoxification of every pyrethroid in mammals and of at least some pyrethroids in insects and fish. The sites of oxidation (Figure 1) and the rates vary with the pyrethroid structure and with different species (25, 138). Table 1 gives structure-biodegradability relationships for pyrethroid oxidation by mouse liver microsomal systems (25). The cyanophenoxybenzyl pyrethroids are oxidized more slowly than the other compounds. Some isomer specificity is involved in the sites of oxidation, but relatively little in the overall rates of metabolism. The methyl group within the chrysanthemate isobutenyl and gem-dimethyl substituents undergoing oxidation is often governed by the geometrical (*cis/trans*) and optical (1R/1S) configuration of the acid (139, 140). On replacement of the chrysanthemate isobutenyl group by the dihalovinyl group, only the geminal-dimethyl substituent remains for oxidation in the acid moiety (113–116).

Piperonyl butoxide (Figure 2), the most important pyrethroid synergist and a classical MFO inhibitor (141–143), increases the toxicity of all pyrethroids to houseflies and some other insects. At high doses it synergizes

pyrethrin *I* by 300-fold and deltamethrin by 10-fold to houseflies. It also synergizes the ip toxicity of *cis*-resmethrin, the cypermethrin isomers, and deltamethrin by 3- to 25-fold to mice (24). Other oxidase inhibitors may also be potent synergists (141) but are not commercially important. MFO induction by phenobarbital reduces the toxicity of fenpropathrin to rats, and TOCP does not potentiate its toxicity, which suggests that with this pyrethroid oxidation is more important than hydrolysis (144).

Relation to Selective Toxicity

The importance of metabolism in the selective toxicity of pyrethroids is suggested by species differences in the rates of detoxification in vivo, the activities of detoxifying enzymes in vitro, and the response to detoxification inhibitors as synergists. Selectivity is conferred more by differences in rates of detoxification than by species variations in the molecular sites of metabolic attack. For instance, esterases and oxidases effective in pyrethroid metabolism appear to be more active from mammalian liver than from fish liver or insect sources. However, such comparisons are of limited value because the enzymes are not always assayed under optimal conditions, and endogenous inhibitors interfere in some cases. Elevated esterase and oxidase levels in resistant strains may confer pyrethroid resistance in houseflies (145, 146) and other insects (30). The natural tolerance of green lacewing larvae to pyrethroids is due in part to a high rate of esterase detoxification (26).

Synergism studies reveal that metabolism is a significant factor in the low toxicity to mice of fenvalerate and [1R,*cis*]-resmethrin, but not of the 1R, *trans* isomers of resmethrin, phenothrin, and permethrin (24). *trans*-Permethrin is hydrolyzed in the relatively insensitive rats and mice and also in the much more sensitive houseflies, cabbage looper larvae, and rainbow trout. Esterase inhibitors have little or no effect on the toxicity of *trans*-permethrin except with the loopers (133), which suggests that in this case more than others the action of esterases limits the toxicity. *trans*-Resmethrin is not toxic to mice even when they are pretreated with esterase or oxidase inhibitors (124), which suggests a tolerance mechanism other than detoxification. In confirmation, ic-administered [1R,*trans*]-resmethrin has a half-life value of $>$ 1 hour in mouse brain, so its low ic toxicity is not attributable to rapid metabolism (18). The low mammalian toxicity of [1R, *trans*]-resmethrin, -phenothrin and -permethrin is therefore probably due to low nerve sensitivity.

SECONDARY EFFECTS AND CHRONIC TOXICITY

Pyrethroids at sublethal doses have pronounced behavioral effects on insects as flushing agents, knockdown agents, and antifeeding agents (23, 31).

They have little if any effect on mammals when used at insecticidal doses (147, 148).

Fenpropathrin, cypermethrin, and fenvalerate induced transient facial sensory symptoms in exposed workers without any accompanying abnormal neurological signs (149). Crude pyrethrum extract contains an allergenic factor(s) causing dermatitis particularly in persons sensitive to ragweed pollen; this impurity is removed in current commercial pyrethrum extract (148, 150). In another type of phenomenon, resmethrin aerosols and residues develop a very disagreeable odor due to a photodecomposition product, phenylacetic acid (151).

Pyrethrins and pyrethroids give exceptionally high "no-effect" levels in chronic feeding studies with mammals (147, 148). Marginal induction in rats of hepatic cytochrome P-450, related cytochromes, or MFO enzymes occurs at high dietary levels of pyrethrum extract (152, 153) and permethrin (154). On the other hand, pretreatment with cypermethrin and fenvalerate does not increase the activity of hepatic MFO enzymes (154, 155). Thus, the pyrethroids appear in general to be either weak inducers or noninducers.

No evidence is available for pyrethroid induction of teratogenesis in mammals (140, 147, 156). Mutagenesis assays of many types have failed to reveal problems for pyrethroids (140, 147, 156). This is of particular interest for pyrethroids with the dihalovinyl substituent because of the partial structural similarity to vinyl chloride. Allethronyl esters are a possible exception since allethrin is detected as a mutagen in the Ames *Salmonella* assay and the chromosomal aberration test in Chinese hamster cells, in the latter system when tested with the liver S9 mix for activation (157). This finding may be attributable to impurities resulting from the conversion of allethrin (and terallethrin) in very low yields to the allethrin photoproduct shown in Figure 2 and to related compounds mutagenic in the Ames assay (158).

Pesticide registration procedures require extensive tests for possible carcinogenic effects. High dietary levels (1000–10,000 ppm) of pyrethroids in subacute and chronic studies invariably cause some histopathological changes in liver (147). The scope of pyrethroid registrations will ultimately depend on the results of the chronic feeding studies and the interpretation of the lesions, if any, observed.

CONCLUSION

Pyrethrin *I*, the principal insecticidal component of pyrethrum flowers, served as the prototype for many synthetic pyrethroid insecticides developed by isosteric modifications of substituents for improved potency and stability. Pyrethroids are an increasingly diverse class of chemicals characterized by their similarity in overall configuration to pyrethrin *I* and their high insecticidal activity. Two types (I and II) of pyrethroid action are

evident based on poisoning symptoms and nerve disruptions. The Type I syndrome generally involves hyperactivity and tremors in both invertebrates and vertebrates. Compounds causing this syndrome produce repetitive firing following stimulation in isolated nerve preparations by affecting axonal sodium channels. Type II symptomology, produced by compounds with cyanophenoxybenzyl substituents, involves hyperactivity, incoordination, and convulsions in insects, and clonic seizures with sinuous writhing in mammals. In insects the Type II effect is associated with long nerve discharges rather than repetitive firing and is probably due either to nerve membrane depolarization or a synaptic action. The Type II syndrome appears to involve an action at the GABA receptor/ionophore complex based on pharmacological, toxicological, and electrophysiological observations. Diazepam and mephenesin ameliorate the toxic effects of pyrethroids, possibly by facilitating inhibitory pathways. Nerve insensitivity is a common cause of resistance in pest populations and is also involved in the natural tolerance of some nontarget species. The metabolic pathways of pyrethroids vary relatively little with species, but differences appear in the rates of esterase and oxidase attack and the sites of oxidation and types of conjugates formed. Esterase and oxidase inhibitors increase the potency of pyrethroids when metabolism is the limiting factor in toxicity. Problems of acute and subacute toxicity to birds and mammals are generally less with pyrethroids than with other classes of insecticides. The most selective pyrethroids are potent insect neurotoxicants that possess little or no action in the mammalian nervous system and that undergo rapid metabolism in mammals, but not in insects.

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