Chapter 7

Avermectins: Biological and Pesticidal Activities

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The avermectins, which show highly potent, broad spectrum of activities against plant parasitic mites, insects and nematodes were discovered in a screening program for natural products of microbial origin. The successful characteristics of this program are discussed. The GABAergic mode of action of the avermectins is unique. Other novel biological properties include: rapid photodegradation of foliar surface deposits, translaminar activity which maintains a pesticidal reservoir within the leaf; sublethal effects on organisms, such as debilitated feeding and reduction in fecundity; and virtual immobility and microbial decomposition in soil.

The discovery of the avermectin family of macrocyclic lactones produced by the soil actinomycete *Streptomyces avermitilis* marks an instructive chapter in the search for natural products of microbial origin. They were not found in a generalized, broad spectrum screen, but in one which had demonstrable elements of rationale and specific objectives. In discussing the characteristics of the successful screening program which led to the discovery of the avermectins at the Merck Sharp and Dohme Research Laboratories, Campbell *et al.* (1) point out that the discovery "..was by no means serendipitous; those who were seeking found what they sought". Their account and those of Stapley and Woodruff (2) and Woodruff and Burg (3) give the details of the initiation and organization of the screening efforts and their denouement as the avermectins.

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The avermectins were discovered in an anthelmintic screening program in which microbial fermentation broths were tested in mice against the nematode Nematospiroides dubius. Two characteristics of this screening program are worth mentioning. First, instead of in vitro, "rationalist" tests such as target enzyme inhibition or receptor binding, the fermentation broths were tested by being administered in diet to nematode-infested mice; even though such an in vivo approach was expensive, it simultaneously tested for efficacy against a parasite and toxicity to the host, which contributed to the speed of further work on the active entities. Second, a deliberate choice was made to emphasize the selection of microorganisms of unusual morphological traits and nutritional requirements (2). Indeed, the cultures of S. avermitilis have characteristics which -- including brownish-grey spore masses, smooth spore surface, sporophores forming compact to slightly open spirals and presence of melanoid pigments -- are unlike those of any other previously described species of Streptomyces. Burg et al. (4) have given the taxonomic description and the fermentation procedures for S. avermitilis.

Among the avermectins, avermectin B_1, and to a lesser extent avermectin B_{2a}, have been studied with reference to plant parasitic mites, insects and nematodes. Since the introductory summary by Putter et al. (5), a limited review of the agricultural miticidal and insecticidal activities of avermectin B_1 has been published by Dybas and Green (6). More recently, Strong and Brown (7) have compiled a comprehensive review of the literature on the agricultural and veterinary insecticidal activities of the avermectins. In the context of this symposium, I intend this article not as a comprehensive review but as a way of discussing some of the unique biological properties of the avermectins in relation to their activities against nematodes, mites and insects of agricultural importance.

Chemistry and Nomenclature

The avermectins comprise a complex of 8 discrete but closely related macrocyclic lactones. Within this complex there are four major components --- avermectins A_{1a}, A_{2a}, B_{1a} and B_{2a} and four minor homologous "b" components A_{1b}, A_{2b}, B_{1b} and B_{2b}. Mixtures of the homologous substances containing approximately 80% or more of the "a" and 20% or less of the corresponding "b" components are usually referred to as avermectin A_1, avermectin B_1, avermectin A_2, and avermectin B_2.

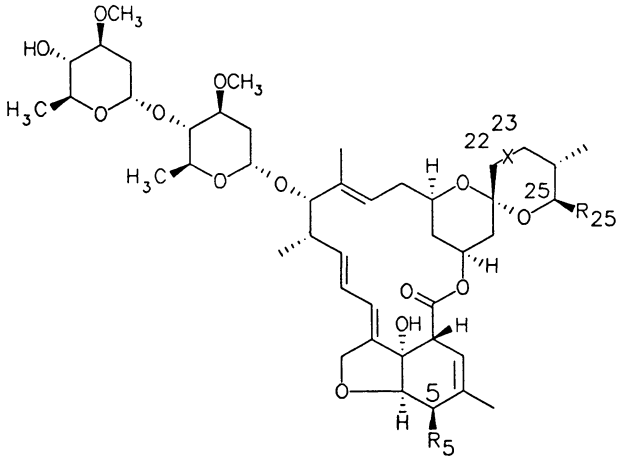
A composite structure of the avermectins is given in Figure 1. It consists of a rigid 16-membered lactone ring system, a spiroketal forming two 6-membered rings, and a cyclohexene diol or methoxycyclohexenol cis-fused to a five-membered cyclic ether. In addition, the structures are characterized by a disaccharide substituent consisting of two identical monomers, alpha-L-oleandrose, coupled to carbon-13 through an oxygen bond.

The large "A" designation refers to the avermectin components in which a methoxy group is present at C-5 and the large "B" refers to the corresponding C-5 hydroxy analog. The subscript "1" is used to identify those components with a 22,23-double bond. The subscript "2" identifies those components with a 23-hydroxyl group. Both "A" and "B" series of components are further characterized by the presence of a secondary-butyl substituent in the 25-carbon position, while the minor homolog contains an isopropyl substituent.

Details of the steps leading to the elucidation of the structures of the avermectins have been published earlier (8,9). Fisher and Mrozik (10) give a comprehensive review of the chemistry of the avermectins and of a complex of 13 closely related compounds known as milbemycins which were isolated from S. hygroscopicus by Japanese researchers (11, 12, 13). A notable difference between the milbemycins and the avermectins is the absence of the 13-hydroxy disaccharide substituent and saturation at the 22,23-positions in all the reported milbemycin compounds. Another major difference is the presence of methyl and ethyl groups attached to C-25 of the milbemycins while the avermectins have secondary butyl and isopropyl groups.

While the avermectins as a class are active against nematodes, insects, mites and other arthropods, they show differences in terms of degrees of activity (6). Components of the "B" series are more biologically active than those of the "A" series. Among the "B" series, avermectin B_1 (containing 80% or more of avermectin B_{1a} and 20% or less of avermectin B_{1b}) has been predominantly studied as an agricultural acaricide and insecticide. Avermectin B_{2a}, and its soil metabolite known as avermectin B_{2a}-23-ketone have been studied for their soil nematicidal activities. A synthetic derivative of avermectin B_1, 22,23-dihydroavermectin B_1, known by the generic name ivermectin has been developed for veterinary and human health uses (14, 15, 16, 17).

The word "ABAMECTIN' has been accepted as the nonproprietary common name for avermectin B_1 (18, 19). It is currently marketed as Avid and Vertimec which are the trade



AVERMECTIN A : $R_5 = OCH_3$ B : $R_5 = OH$

1 : X = $-CH=CH-$ 2 : X = $-CH_2-\overset{OH}{\overset{|}{C}}H-$

a : R_{25} =  b : R_{25} = 

IVERMECTIN : $R_5 = OH$ X = $-CH_2-CH_2-$ R_{25} =  AND 

AVERMECTIN B_{2a} 23-KETONE : $R_5 = OH$ X = $-CH_2-\overset{O}{\overset{\|}{C}}-$ R_{25} =  AND 

Figure 1: Structures of the avermectins (Courtesy of H. Mrozik, Merck and Co., Inc.).

names for an emulsifiable concentrate containing 1.8% w/v of abamectin for use against plant parasitic mites and insects in agriculture. Affirm is the trade name for a bait formulation containing 0.011% w/w of abamectin for use against the red imported fire ant Solenopsis invicta. It is also used as a cattle anthelmintic and ectoparasiticide as a 1% w/v injectable under the trade name Avomec in Australia.

Early pharmacological, biophysical and biochemical studies used several avermectins such as avermectin B_1, the B_{1a} component alone and ivermectin (20). Observations from these studies and the structure-activity relationships (10) show there is no evidence for qualitative differences in the mode of action of the avermectins. Therefore, in this discussion, the word 'avermectins' will be used as a generic reference.

Mode of Action

Early observations on the selective biological activities of the avermectins were instrumental in understanding their mode of action. While showing strong anthelmintic, insecticidal and acaricidal activities, they were ineffective against Platyhelminths such as flukes and tapeworms. Avermectins were also inactive against bacteria, yeasts and protozoa. An earlier report that a methanol extract of a culture of S. avermitilis inhibited some filamentous fungi by interfering with chitin biosynthesis (21) has been proved to be erroneous by Onishi and Miller (22) who showed that oligomycin (23) and an antifungal polyene produced by the organism accounted for the antifungal activity and that pure avermectin B_1 did not affect the fungi or their chitin metabolism. Similarly, Gordnier et al. (24) have been unable to detect inhibition of chitinase or chitin synthetase derived from a variety of insects.

Thus the conclusion was that there must be a specific target for the avermectins' activity in nematodes and arthropods which is either absent or inaccessible in fungi, bacteria, and Platyhelminths. Wang (25) gives an excellent, protagonist's account of the efforts which led to the conclusion that the avermectins act on invertebrates by potentiating the activity of gamma-aminobutyric acid (GABA) which is an inhibitory neurotransmitter in their nervous systems. Wright (20) gives a comprehensive review of the work done on understanding the mode of action of the avermectins and Stretton et al. (16) have reviewed the mode of action with specific reference to nematodes. Since a detailed analysis of the work done to understand the mode of action is out of the scope of this article, I will provide a summary of the current knowledge on the mode of action in relation to the observed biological activities.

Electrophysiological research done soon after the discovery of the avermectins with the nematode Ascaris (26) and the crustacean arthropod lobster (27) showed that avermectins functioned as post-synaptic agonists of GABA, potentiating the GABA-mediated chloride ion channel conductance. Corollary work (28) demonstrated that avermectins markedly stimulated the release of GABA from rat brain synaptosomes which had been preloaded with radiolabelled GABA. Further work on the GABA-receptor preparations derived from mammalian brain (28, 29) showed that avermectins bind to GABA-receptors and also increased the affinity of these receptors for benzodiazepams (30). It is also known that GABA itself also stimulates the binding of benzodiazepams to the GABA-receptors (31). Since both GABA and the avermectins stimulate benzodiazepam binding, one can infer that avermectins, like GABA, open the chloride channel of the GABA-receptor and thus avermectins behave as GABAergic agonists.

Therefore, with reference to nematodes and insects, the current explanation for the mode of action is that avermectins stimulate the release of GABA from nerve endings and then enhance the binding of GABA to receptor sites on the post synaptic membrane of an inhibitory motoneuron in the case of nematodes, and on the post-junction membrane of a muscle cell in the case of insects and other arthropods. The enhanced GABA-binding results in an increased flow of chloride ions into the cell with consequent hyperpolarization and elimination of signal transmission. An indirect yet strong evidence that GABA plays a role is that the effects of avermectins on invertebrates can be reversed by the chemicals picrotoxin or bicuculline (32) which act as GABA-antagonists by slightly different mechanisms (33, 34). Picrotoxin noncompetitively antagonizes GABA (35), while bicuculline competitively antagonizes by displacing GABA from the binding sites on the receptor (36).

While the GABAergic mechanism has been largely accepted, there are also indications that avermectins have more than one mode of action. At least two distinct sites of action, differing in their location, pharmacological behavior or both, have been recognized in arthropods (37, 38) and nematodes (26, 39). Stretton et al. (16) conclude: "Whether there are only two sites in each system, and whether the two sites are comparable in different phyla (Nematoda and Arthropoda) is not clear. A common thread in many cases is that there are correlations between AVM (sic) sensitive loci and the presence of (gamma)-aminobutyric acid (GABA) sensitive mechanisms involving a chloride ion permeability change".

Activity Against Soil Nematodes

The biological activities of the avermectins on plant parasitic nematodes have mostly been studied in terms of their gross effects on the movement and infective behavior of the juveniles of the rootknot nematodes Meloidogyne spp. Juveniles of M. incognita exposed to a 120-mM aqueous solution of abamectin or B_{2a}-23-ketone showed a three-phase response consisting of initial loss of movement within 10 minutes while being responsive to touch, partial recovery within 30 minutes of exposure and irreversible loss of movement after 2 hours (32). It is not known if the intervals between responses are dependent upon the concentration of the chemical in the solution. The initial loss of movement in M. incognita may be reflective of the avermectins' activity as GABA-agonists at the inhibitory synapses in nematodes (40); this possibility has been supported by the observations, as mentioned earlier, of Wright et al. (32) that GABA antagonists picrotoxin and bicuculline counteracted the inhibitory effects of avermectins on the locomotion of the juveniles. Under soil free conditions B_{2a}-23-ketone reduced the invasion of cucumber roots by M. incognita juveniles and their further development at concentrations much lower than were needed to immobilize them. It has been proposed in this context that avermectins affect the root-seeking behavior of juveniles, a mode of action also suggested for organophosphorus and carbamate nematicides (41). Avermectin B_{2a} did not affect the post-invasion development of M. incognita juveniles in tomato roots exposed to 1.0 ppm w/v solutions 48-72 hours post-invasion (16). Abamectin and avermectin B_{2a} showed only limited downward movement: spraying of aerial parts of tomato plants with 1000 ppm w/v solutions resulted in only minor inhibition of root galling (Merck and Co., Inc., unpublished). Eggs of M. incognita placed in a 0.1 ppm w/v aqueous solution of avermectin B_{2a}-23-ketone failed to hatch, but when they were rinsed in water 96 hours later, hatching occurred, which Wright et al. (41) suggest indicates that embryogenesis proceeded normally and that hatching was halted by the immobilization of the juveniles by the chemical. Avermectins begin to immobilize nematodes within 10 minutes of exposure (42, 32), while acetylcholinesterase inhibitors such as oxamyl cause hyperactivity. This is probably the reason behind the reduced oxygen consumption by juveniles of three Meloidogyne spp. exposed to 0.05 ppm solutions of avermectin B_{2a} (43).

When incorporated into soil, avermectin B_{2a} was slightly more potent than abamectin and was about 10-30 times more potent than several organophosphate and carbamate nematicides against M. incognita (44, 45). The longer soil residual activity of avermectin B_{2a}, with a half-life in soil of

2.5-3.0 days, has been ascribed to its conversion by soil microorganisms to avermectin B_{2a}-23-ketone (5), itself having a soil half-life of about 30 days (46). Interestingly, Preiser et al. (44) determined that the nematicidal potency of B_{2a}-23-ketone was slightly greater than that of B_{2a}; it is possible that the greater soil nematicidal potency B_{2a} is a combination of its own nematicidal activity combined with that of its soil metabolite.

Stretton et al. (16) have reviewed the microplot and large scale field trials done with avermectin B_1, B_{2a} and B_{2a}-23-ketone. The salient observation was that at soil application rates ranging from 0.168 to 1.52 kg ai/hectare all the avermectins were effective in controlling the rootknot nematodes. However, the differences in efficacy among the avermectins observed in the controlled greenhouse experiments do not obtain in the large scale field trials, at least among the limited number done so far. In this context, the influence of the physico-chemical properties on the behavior of the avermectins in soil should be considered. The water solubility of abamectin is 7.8 ppb w/v and its leaching potential through many types of soil is extremely low (47, 48), with the result that the chemical does not move into the rhizosphere readily unless mechanically incorporated to a sufficient depth. These factors have limited the successful use of the avermectins as soil nematicides. Paradoxically however, the physico-chemical properties also confer many potential advantages upon the use of the avermectins as nematicides. Their rapid degradation and poor mobility suggest that field applications would not result in persistent residues or contamination of ground water (48).

Photodegradation

Extensive and rapid photodegradation after application to plant surfaces appears to be a prominent characteristic of abamectin.

Studies on the fate of tritiated abamectin after application to cotton leaves showed that the compound was rapidly degraded on leaf surfaces; at 48 hours post-treatment, only 18.4% of the recovered radioactive material was abamectin (48). Jenkins et al. (49) applied abamectin to greenhouse-grown chrysanthemums at 22.4 and 44.8 g ai/hectare and determined that dislodgeable abamectin residues on the leaf surfaces were reduced by 90-98% by 24-72 hours postapplication (Figure 2). While the dynamics of the degradation would vary depending upon the morphology of the leaf surface and the intensity of the light, it is clear that the surface deposits of abamectin are degraded rapidly.

The rapid disappearance of the surface deposits of abamectin is an advantage in terms of nontarget, beneficial organisms. An example of this can be seen in the case of foraging honeybees (Figure 3). Field-grown alfalfa foliage treated with abamectin at different rates was collected at various post-treatment intervals. Bees were then kept in continuous contact with this foliage for 24 hours at which time their mortality was assessed. There was a steady decline in mortality, resulting in virtually no mortality at 36 hours post-treatment (50).

Translaminar Activity

In spite of the observed rapid degradation of the surface deposits, abamectin shows high post-application residual activity on leaves. This anomaly can be explained as being due to the translaminar activity of abamectin.

Translaminar activity of chemical refers to the movement of chemical from the treated surface into the leaf so that insect or mite pests feeding on the untreated surface would be affected (51, 52). In the context of abamectin, it can be proposed that while the surface deposits are quickly depleted (48, 53), the amount which has penetrated into the leaf forms a within-the-leaf reservoir, which give abamectin its residual miticial activity (6).

Wright et al. (54) have demonstrated such translaminar activity in bean, cotton and chrysanthemum leaves. In their experiments, abamectin was applied to the upper or lower surface of the leaf and mites were confined on the opposite surface. The differences in the activity of abamectin among the three plants are possibly due to structural differences in the cuticular waxes; Wright et al. (54) do point out that bean leaves have the least and chrysanthemum the most waxy cuticle. There were no significant differences in translaminar movement whether the chemical was applied to the upper and lower surface. This observation is of particular interest because penetration of chemicals into leaves is usually assumed to be greater through the lower than the upper leaf surface (55, 56).

Little is known about abamectin's patterns of movement within the leaf after it has penetrated the cuticle or whether its presence in the leaf mesophyll is apoplastic or symplastic or both. However, plant parasitic mites are destructive feeders and withdraw the contents of the palisade cells and those of the mesophyll (57, 58) and thus seem to ingest sufficient amounts of abamectin associated either with the cytoplasm or the cell walls. The depth of penetration need not extend from the treated upper epidermis to the untreated lower epidermis (or vice versa) where mites feed: it is known that the stylets of the tetranychid mite

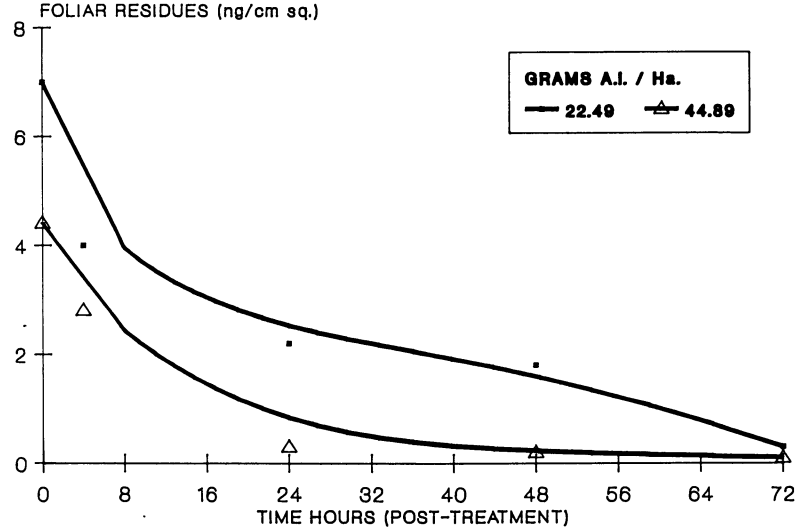


Figure 2: Foliar dislodgeable residues (expressed as nanograms/cm^2) of abamectin applied at two different rates to chrysanthemum leaves, determined at different times after application.(Adapted from ref. 49).

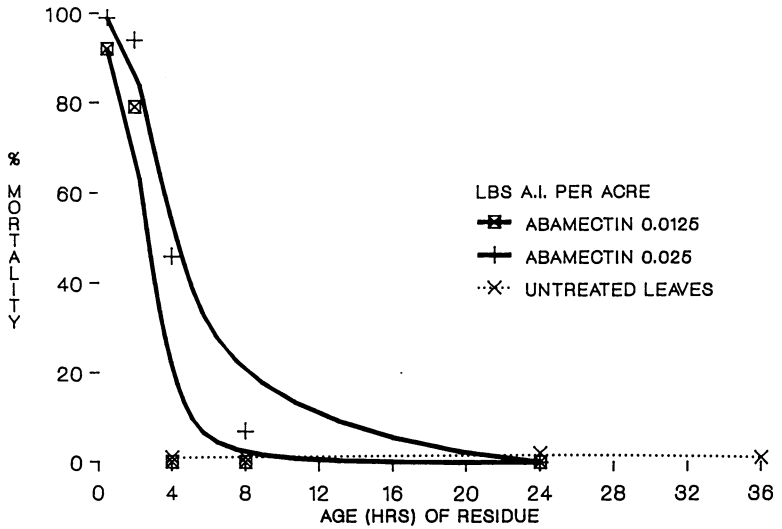


Figure 3: Effects on honeybees (Apis mellifera) of residues of abamectin applied at two rates onto alfalfa foliage. Bees were introduced onto treated foliage bearing residues aged for different time periods (Adapted from ref. 50).

Tetranychus urticae can penetrate the leaf to a depth of 70-100 um on a bean leaf of approximately 180 um thickness (58).

Behavior in Soil

Gullo et al. (46) discovered that avermectin B_{2a} incubated in a sandy loam soil under greenhouse conditions was rapidly degraded, with a half-life of 2.5 to 3.0 days, to a metabolite identified as a 23-keto derivative formed by soil. This metabolite was formed by soil microorganisms: in sterilized moist soil after 13 days, less than 1% of the added B_{2a} was converted to the metabolite compared with 44% under non-sterile conditions. At least three microorganisms capable of such transformation have been reported (46).

Similar studies on the fate of tritium-labeled avermectin B_{1a} in three kinds of soil have shown that under aerobic conditions it was degraded at a rapid rate, with a half-life in sandy loam of 14-28 days, in clay 25-56 days, and in coarse sand 56 days. The major soil degradation product was an equilibrium mixture with a ratio of 1:2.5 of the 8-alpha-hydroxy derivative and the corresponding open-ring aldehyde derivative (48). No further work regarding the nematicidal activity of these metabolites has been reported.

Lethal And Sublethal Activities

Avermectins differ fundamentally from other neuroactive pesticides, probably in keeping with their GABAergic mode of action, in that they do not cause hyperactivity in the affected organisms. Immobilization of nematodes soon after exposure to avermectins as reported by Wright et al. (32) was also reported earlier (5) in the case of mites and insects. The effects of such a mode of action, depending upon the degree of exposure to the chemical, can be lethal or sublethal.

As Strong and Brown (7) observe, there is no satisfactory definition of a "lethal effect"; however, death in the sense of an irreversible effect, described, for example, by Deecher et al. (59) as failure to respond to tactile stimulus, occurs in 72-120 hours after sufficient exposure to abamectin. The comparative symptoms of toxicity of abamectin and the pyrethroid cypermethrin when applied topically to the lepidopteran insect cotton bollworm (Heliothis zea) larvae are illustrative (B. I. Goll, personal communication). In the case of abamectin, there was flaccid paralysis, cessation of feeding, arrested ecdysis manifested as the presence of head capsule at the tip of the mandibles and a silvery grey color of an otherwise unaffected body with the presence of heartbeat observable in the third posterior

abdominal segment. The presence of heartbeat has also been observed in H. zea adults which have ingested abamectin (60). Cypermethrin, in contrast, resulted in rapid convulsions and a shrunken larval body accompanied by an intense darkening of the cuticle.

Apart from the direct toxic effects resulting in mortality, an insecticide or a miticide can have other nonlethal, yet deleterious effects on the organism. Moriarty (61) described many such effects induced by a number of earlier insecticides. Kumar and Chapman (62) recently reported on such sublethal effects such as the inhibition of feeding, developmental disturbances and reduction in fecundity in the diamondback moth Plutella xylostella. Knowles (63) has described the effects, other than lethality, of some formamidines on plant parasitic mites.

Among such sublethal effects of the avermectins, reduced fecundity has attracted particular attention. Lofgren and Williams (64) observed that abamectin, when fed to the colonies, inhibited the reproductive capacity of the queens of the red imported fire ant S. invicta, with the resultant truncation of the colonies. Subsequently, Glancey et al. (65) histologically examined the ovaries of queens from colonies treated 22-weeks earlier and described the damage as: hypertrophy of the squamous epithelium which sheathes the ovarioles and pycnosis of the nurse cell nuclei which resulted in complete absence or reduction in the numbers and size of eggs produced.

There have also been reports of reduced fecundity among survivors of lepidopteran insects exposed to abamectin. Adults of the codling moth Cydia pomonella developing from larvae exposed to abamectin produced significantly fewer eggs (66). Beach and Todd (67) fed abamectin to male and female adults of soybean looper Pseudoplusia includens and subsequent matings of such insects resulted in reduced fecundity and fertility. A variation has been that of Robertson et al. (68) where fertility but not fecundity was affected in matings of males and females of the western spruce budworm Choristoneura occidentalis developed from larvae exposed to abamectin. Sublethal effects have been reported to include post-embryonic development of some insects; Heliothis virescens and H. zea larvae which survived abamectin treatment continued molting but did not survive pupation (69). The consequence was that even at doses below LD_{50}, few adults emerged from the pupae. Sublethal doses resulted in prevention of pupation in the eastern yellow jacket Vespula maculifrons (70) and extension of the pupal period in codling moth C. pomonella larvae (66).

An insecticide's effect on reproductive potential can be caused by a lowered incidence of mating, a shortened life

span, the suppression of the reproductive organs and a direct toxic effect on the eggs (62). There is no evidence that abamectin affects insect or mite reproductive tissues directly. Even the ovarian regression in S. invicta observed by Glancey et al. (65) should be considered from the perspective that at the time of their observations 22 weeks had elapsed since treatment. The observed effects could have been due to starvation of the queen and the resultant dysfunctional changes in the general metabolism. The introduction of controls consisting of untreated but starved queens and histological observations at shorter post-treatment intervals would clarify this report. In the absence of direct observations on oogenesis or embryogenesis, the reduced effects of abamectin on fecundity will have to follow the obverse of the hormoligosis hypothesis proposed by Luckey (71) in that sublethal poisoning is likely to reduce the general fitness of the insects or mites and thereby their reproductive capacity and even the post-embryonic development.

A result of immobilization is the cessation of feeding, which has been termed as feeding inhibition. Strong and Brown (7) object to such a description on the reasoning that antifeedant properties should not be ascribed to a chemical unless such properties can be separated from general toxicity and debilitation. In my experience, in all instances where immobilization or cessation of feeding have been observed, death eventually resulted. It appears that an observed sublethal effect is really the beginning of the lethal effect. The relationships between the concentration of the chemical, speed of activity on different insects and the consequences of debilitated feeding, for example, the reduction in the leaf area consumed, are yet to be studied.

Differential Toxicities

Among the insects which were recorded as being affected by abamectin were three lepidopteran insects against which abamectin showed differential toxicity (5). The foliar ingestion toxicity LC_{90} values (for neonate larvae) were 0.02 ppm for the tomato hornworm Manduca sexta, 0.75-1.2 ppm for the cabbage looper Trichoplusia ni and 1.5 ppm for the southern armyworm S. eridania. Further research on the toxicity of abamectin to lepidopteran insects has shown some interesting characteristics of abamectin.

Anderson et al. (72) confirmed the observation by Putter et al. (5) that S. eridania was less sensitive to abamectin than H. virescens, both in treated foliage ingestion by neonate and topical applications to third instar larvae among the Heliothis spp. H. virescens is more susceptible to abamectin than H. zea (73, 74). Bull (69) confirms the

differences in the sensitivities of H. virescens and H. zea and also demonstrates the marked insensitivity of the fall armyworm S. frugiperda.

The reasons for the differences in the toxicity of abamectin to the different lepidopteran insects are not clear. Bull (69), by using orally administered tritiated-B_{1a}, observed that physiological processes like absorption from the larval midgut, metabolism and excretion of the metabolites were slower in H. virescens than in H. zea or S. frugiperda. Similarly, significantly more tritiated avermectin B_{1a} was recovered from the heads of H. virescens. Neither slower metabolism nor faster accumulation in the head can categorically explain the greater sensitivity of H. virescens, considering that there were no significant differences between H. zea and S. frugiperda in the metabolism of avermectin B_{1a}. There were substantial differences between them in their susceptibility to avermectin B_{1a}. This aspect can be better understood by testing the hypothesis that differential sensitivity is related to differences in the affinity to, and therefore the accumulation of, abamectin at the GABA-receptors in the insects (69).

Conclusion

In summarizing the biological-pesticidal activities of the avermectins, two paradoxical properties can be noted. First, foliar surface deposits are rapidly degraded with the result that many beneficial organisms do not encounter the toxic entity significantly. However, avermectins seem to penetrate the leaf lamellae and be available as a pesticidal reservoir against mites and insects. Second, while they are potent against soil nematodes, they are also nearly insoluble in water and have an extremely low leaching potential. A clearer understanding of the mechanisms behind the leaf cuticular penetration would be helpful in finding ways to increase the toxic reservoir within the leaf while the surface deposits remain low, with the attendant advantages. Similarly, defining the mechanisms of soil binding would be helpful in finding ways to increase the avermectins' mobility and presence in soil water to act against nematodes.

The sublethal activities of the avermectins also need further scrutiny. For example, is the reduction in fecundity a direct effect or an indirect one due to the effect of the avermectins on the 'fitness' of the organism? The consequences of reduced fecundity and debilitated feeding need to be quantified in terms of the effects on the pest population dynamics. More research along the lines that Bull (69) suggests can explain the mechanisms behind the lesser susceptibility of some economically important lepidopteran insects.

The avermectins mark an important event in the search for natural products of microbial origin which are useful in agriculture. However, they may be only the beginning. Given their broad range of pesticidal activities, it is possible that future screening programs or semisynthetic modifications will yield entities which have one or more characteristics such as exclusive miticidal or insecticidal activity, enhanced cuticular penetration, resistance to photodegradation and greater soil mobility.

Acknowledgments

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