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The Future of Chemical Pest Control

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ABSTRACT The agricultural industry is beset by continuing demands to decrease the use of pest control agents which employ toxic modes of action. Although there are real problems of pesticide resistance, and sometimes overuse or redistribution in the environment, much criticism results from a lack of appreciation of how small is the risk involved. Whatever the background reasons, research and development for pesticide alternatives, particularly within Integrated Pest Management systems, is clearly of high priority. Currently available approaches, including use of natural products and molecular biology, are often regarded with naïve optimism and require critical appraisal. For the future, methods of pest control based on chemicals with non-toxic modes of action (e.g. pheromones) continue to offer promise but, for widespread use, will require their integration with biological agents and development by means of plant molecular biology.

KEY WORDS Natural products, insecticide resistance, semiochemicals, chemical ecology, pheromones, Integrated Pest Management, stimulodeterrent diversionary strategy, plant molecular biology

INTRODUCTION

The efficient production of food, fibres and other agricultural produce requires effective pest control. For the present, and indeed for the immediate future, reliance will be on broad-spectrum eradicant pesticides. The existing range of agents is largely confined to pesticides that, when used appropriately, are safe both to man and the environment. Nonetheless, further restrictions, particularly where adverse environmental effects are suspected, will be introduced over the next few years. In the longer term, new approaches will be available. These will involve novel types of chemicals including more selective toxicants, but also compounds with regulatory modes of action. A particularly important aspect of these developments will be the integration of the various types of crop protection agents and thereby the advancement of true Integrated Pest Management(IPM). A important stimulus for the development of new approaches to chemical pest control is the public perception that extreme hazards arise from the currently used broad-spectrum pesticides. In fact, such hazards are relatively small compared with many other aspects of human activity and where there are real problems, these usually arise from misuse. However, the more intrinsically safe and selective crop protection agents become, the less chance there is of misuse causing problems. In addition, there is a scientific stimulus to develop new approaches that exploit natural regulatory processes as opposed to toxicity.

A real and compelling reason to improve chemical pest control is the development of resistance. Many have advocated the development of novel pesticides to solve this problem, for example by choosing new target sites for pesticide action, by exploiting natural products, or by use of molecular biology. However, these proposals require critical assessment. In the face of pesticide resistance, there is no potential for sustained pest control based solely on the novelty of the pesticide. Nonetheless, novelty in chemical approaches to pest control can be a component of integrated resistance management, an important component of IPM. This can be provided as a novel molecular structure not metabolized by pathways already enhanced in resistant insects(metabolic resistance), or which can interact with a target site modified during development of resistance to avoid interaction with the toxicant(target site resistance). Alternatively, compounds with complete novelty in structure and target site can be sought (Pickett 1992).

In terms of "natural" versus " synthetic", natural products may not be as benign as some imagine. For example, although most natural compounds have not been screened as rigorously as synthetic compounds for human and environmental effects, roughly 50%, a similar proportion to that for synthetics, are found to be carcinogenic in the standard tests(Ames & Gold 1990). Indeed, 99.99% of pesticides that are taken in through our diet are not synthetic compounds but are the natural agents employed by plants in their defence, a large proportion of which are potential carcinogens(Ames et al. 1990).

THE DEVELOPMENT OF NEW INSECTICIDES

The current range of insecticides, principally organophosphates, carbamates and pyrethroids, and some organochlorine compounds still remaining in use, attack the insect nervous system. The pyrethroids interfere, at the sodium channel protein, with axonal transmission of the nerve impulse, whilst the organophosphate and carbamate insecticides affect synaptic transmission (Corbett et al. 1984).

To overcome metabolic resistance mechanisms, the objective would be to produce novel structures which could embody similar target site activity to the parent pesticide. In the case of aphids, predominant as insect pests of temperate agriculture, the main mechanism of resistance is gene amplification to increase production of an esterase enzyme that detoxifies or sequesters pesticides by interacting with ester bonds(Devonshire & Moores 1982). Some compounds, for examples triazamate (Jacopson & Thriugnanam 1991), whilst retaining the original target site activity of interfering with synaptic transmission, resist metabolic decomposition by having a substantially different structure from the conventional organophosphorus or carbamate compounds. To deal with site of action resistance, which can be an important factor in resistance to pyrethroids, new structures must be produced as the site is modified. However, some pyrethroids show a greater ability to deal with such modifications to the target site, suggesting that these very successful insectisides may be further developed to overcome resistance (A.W. Farnham & B.P.S. Khambay, unpublished data). It has been noted that certain isobutylamides, which also affect axonal sodium channels, can show negative cross-resistance, again demonstrating the potential for obtaining compounds that overcome this type of resistance (Elliott et al. 1986). In both metabolic and site of action resistance, the way forward involves understanding, at the molecular level, the nature of changes. Molecular biology studies on the metabolic resistance esterase from aphids is uncovering the mechanism of expression after gene amplification (Field & Devonshire 1992). With site of action resistance against pyrethroids, gene cloning studies are already producing sequences for the sodium channel protein from resistant and non-resistant insects, which it is hoped will prove of value in designing compounds to overcome this type of resistance (A.L. Devonshire & M.S. Williamson, unpublished data).

Alternative approaches are to find new target sites and new molecular structures. A great deal of attention has recently been focussed on the GABAergic systems employing the neurotransmitter γ-aminobutyric acid. However, although the avermectins(Fisher 1990) are highly active in this respect, they retain unexpectedly high mammalian toxicity. New, more simple compounds with a trioxabicyclooctane structure (Casida et al. 1990), and related monocyclo compounds containing sulphur (Elliott et al. 1992, Palmer & Casida 1992), also have this target site but again retain high mammalian toxicity.

Leaving the nervous system as a target, a great deal of attention has been directed at regulation of morphogenesis and cuticle development, since this could yield compounds more specifically directed against insects. Insecticides such as diflubenzuron, teflubenzuron and related compounds were obtained by chemical screening (Anderson et al. 1990), but have highly selective insecticidal activity by interfering with chitin deposition. There are also natural products which are insect chitinase inhibitors (Sakuda et al. 1986), but which have structures too complicated for use as new insecticide leads. Compounds acting as agonists of insect juvenile hormones have also been developed and were originally based on the structures of the hormones (Jennings 1983). More recently, new insecticides, such as pyriproxyfen (Sumitomo Chemical Company Limited), with purely synthetic backgrounds have emerged, but having apparently the same mode of action. Compounds imitating ecdysis hormones are at present largely undeveloped.

Bearing in mind the success story of the development of synthetic pyrethroids from the natural pyrethrins (Elliott 1990), plant-derived natural products have been seen very positively as providing new leads for insecticides. Although rotenone from *Derris* and *Lonchocarpus* species is, by the standards of modern synthetic compounds, a poor insecticide and has high mammalian toxicity, interesting work has for the first time produced a more active analogue (Josephs et al. 1992). The acetogenin insecticides from plants in the Annonaceae (Alkofahi et al. 1988) have received much attention (Rupprecht et al. 1990), but also retain high biocidal activity. Much work has been done on the tetranotriterpenoid insecticides from plants in the Meliaceae, particularly the Indian Neem tree *Azadirachta indica*, but the lead compound azadirachtin (Kraus et al. 1985, Broughton et al. 1986) remains undeveloped, in spite of very sophisticated synthesis investigations (Ley 1990), because of high instability and low insecticidal activity combined with a very complex chemical structure. The literature continues to contain interesting new structures with insecticidal activity, e.g. Klocke et al. 1991, Alexander et al. 1991, but often there are problems of synthesising the polychiral compounds or a high general biocidal activity.

ADVANTAGES OF NATURAL PRODUCTS IN PEST CONTROL

Although the toxicological properties of natural products may not show them to be generally more begin than synthetic compounds, there are some specific advantages arising through there natural origins. These revolve around the fact that they are biosynthesised by pathways necessarily present in living organisms. Such materials could therefore be developed using the new techniques of molecular biology, for example by 1) production by genetically modified fermentation organisms; 2) modifying natural delivery systems; 3) producing transgenic crop plants expressing new pathways or with natural pathways augmented by genetic engineering. Obvious targets are oligopeptides because, as such, they are direct products of single genes. Insect neuropeptides, including relatively low molecular weight peptides, can have very high levels of activity in regulating various processes. Many such processes do not have a life or death role in insects, but recently the diuretic hormone from *Manduca sexta* was identified as an oligopeptide with 41 amino acids (Katoaka et al. 1989). The type of activity involved in this case is promising for development of insect control agents. Insecticidal venom toxins from spiders and Hymenopterans (Bruce et al. 1990), incorporating polyamines combined with amino acids, present interesting targets, as do the antibiotic agents based on peptidic structures from insect pathogenes such as *Metarhizium anisopliae* (Roberts 1981).

For peptide based leads to be developed as toxicants, either the chemistry must be modified by replacing, for example, peptidic linkages where attack by proteolytic enzymes prevents toxic concentrations being achieved (Khambay 1993), or special delivery systems must be used. The latter are available in the form of baculoviruses which can now be genetically modified to carry the gene for an alien protein (Stewart et al. 1991), although this strategy has not yet led to commercial development of these potential toxicants againts insect pests. Modification of crop plants to produce the genes for such materials world be of little value unless the plant had a mechamism for transmitting the agents through the cuticle or peritropic membrane of the gut. However, there are certain toxic proteins, for example the endotoxins of *Bacillus thuringiensis* strains already used as biological control agents, various enzymes e.g. chitinases, and enzyme inhibitors such as the protease inhibitor from the black-eyed bean, which have been successfully developed by expressing the appropriate gene in transgenic plants (Vaeck et al. 1987, Hilder et al. 1987). Futher potential for these approaches is now seen because of the availability of tissue and growth stage specific promoter systems which, by offering alternatives to constitutive expression, will reduce the potential for resistance.

The main defence used by plants growing wild is their secondary metabolism. This presents a difficult target for plant genetic engineering, since secondary metabolites are not gene products but are usually produced by relatively complicated biosynthetic pathways. Nonetheless, transfer of the stilbene synthase gene from the groundnut *Arachis hypogaea* into *Nicotiana tabacum* has allowed augmentation of existing pathways to produce the phytoalexin resveratrol (Hain et al. 1990), which can act against fungal disease. Other similar targets exist where opportunistic use could be made of existing pathways by gene augmentation. For example, sugar beet is in the same family, Chenopodiaceae, as wild plants producing defence based on phytoecdysteroids (Lafont & Horn 1989, Camps 1991). Thus, there is the possibility of the appropriate genes being transferred into sugar beet to produce useful defence compounds.

NEWS REQUIREMENTS FOR INTEGRATED PEST MANAGEMENT

For successful and long term exploitation of new, more selective toxicants, and to realise the full value of the considerable efforts being made to produce crop plants resistant to pests by genetic engineering, true integration of the various approaches must be established from the outset. Thus, pheromones and other semiochemicals should be used to monitor the pest population, host plant resistance utilized to reduce development of disease and pests on the crop, and trap crops employed where pesticides or biological control agents can be applied sparingly and most effectively. However, it should be borne in mind that the public is already suspicious of agents with toxic modes of action. Every effort must therefore be made to replace such materials with those working as regulators, for exmple the semiochemicals that carry signals at sub-toxic levels between different organisms. It should also be remembered that once these regulators have been employed, it is advisable and often necessary to incorporate into the control strategy a biological agent to reduce the population of the pest. Again, to avoid criticisms of using toxic modes of action, biological agents should be chosen that work by pathogenicity rather than by antibiosis.

Approaches involving only regulatory agents, e.g. semiochemicals and pathogens, have been termed push-pull or stimulo-deterrent diversionary strategies (SDDS) (Miller & Cowles 1990, Pickett et al. 1991). Within individual plants, these could employ semiochemicals such as antifeedants or inhibitors of host plant attractants (kairomone inhibitors), to protect the valuable part of the crop. At the same time the pests, possibly by use of food plant attractants and aggregation stimuli, would be aggregated on to a part of the crop where a slow but selective insecticide, or a biological agent such as a fungal pathogen, could be used. Such an approach has now been demonstrated under stimulated field conditions using clerodane antifeedants to protect the growing part of the plant, whilst aggregating coleopterous pests lower down in the canopy where destruction was effected by the insect growth inhibitor teflubenzuron (Griffiths et al. 1991), as a prelude to using a fungal pathogen for biological control. On a lager scale, the harvestable crop is again protected by repellant materials but in addition, a reduction in host plant acceptability would be provided by genetic modification of the secondary pathways that produce attractants. The harvestable crop is then surrounded by a trap crop which also incorporates visual cues, e.g. an early flowering variety, and various attractants including aggregation or sex pheromones for the pest (Pickett et al. 1991). The trap crop sites, or aritificial traps as an alternative, can be chosen so that the fungal pathogen can be kept away from dessicating effects of wind and sunlight and thereby perform much more effectively than normally possible in arable agriculture.

SEMIOCHEMICALS FOR INTEGRATED PEST MANAGEMENT STRATEGIES

To provide the necessary range of semiochemicals for SDDS, it is essential to have a full understanding of pest chemical ecology and this is greatly facilitated by investigating the sensory nervous system. In addition to the electroanntenograph, it is now possible to record from individual sensilla and even single nerve cells whithin insect olfactory and gustatory receptors. Coupling such electrophysiological preparations with high resolution chromatography then offers the prospect of identifying a wide range of semiochemical components of pest chemical ecology. This has already been achieved for olfaction by coupling single cell recordings to high resolution capillary column gas chromatography(SCR-GC)(Wadhams 1990). The coupling between gustatory receptors and liquid chromatography will follow from our laboratory shortly. At present, an SDDS is being established for reducing pesticide use in oilseed rape, *Brassica napus* (Pickett et al. 1989), and the use of SCR-GC can be exemplified by studies on an important coleopterous pest, the seed weevil *Ceutorhynchus assimilis* (Blight et al. 1989). The intact plant produces hundreds of volatile chemicals which can be entrained from the air above the crop using absorbent polymers. When the insects feed on the plant, the spectrum of compounds changes, including the incorporation of metabolites from the insects themselves. However, by recording from individual nerve cells within the antenna of the insect, the picture can be greatly simplified and those compounds likely to be important in the chemical ecology of the pest determined. As expected for a crucifer feeder, the isothiocyanate catabolites of glucosinolates play an important role for *C. assimilis.* Differences in the response to the alkenyl and aromatic isothiocyanates have been observed and it appears that the alkenyl compounds are important in colonisation of the crop and orientation towards the plant, whereas detection of the aromatic isothiocyanates may give the insect an indication of the growth stage. Already it is possible to use compounds indentified in this study to act as lures in water traps(Blight et al. 1992). Many other compounds are detected by the antenna, bur far fewer than the great range produced by the plant. Thus, those studying the behaviour of the pest are presented with a simpler task in terms of numbers of compounds for priority investigation.

It is now being established that aromatic glucosinolates can confer disease resistance and it would therefore be desirable for the harvestable crop to produce the alkenyl glucosinolates catabolites minimally, whilst production of the aromatic glucosinolates in the vegetative parts of plant should be maximised for disease protection. At the same time, there is a need to decrease glucosinolate content in the seed so that it can be effectively used for animal feed after oil pressing. Such a rationally based molecular biology programme has now been established(Dawson et al. 1989a). Already, divergences have been found in the biosynthetic pathways to the alkenyl and aromatic glucosinolates(R.N. Bennett & R.M. Wallsgrove, personal communication) and these are being further investigated to allow appropriate genetic engineering of an oilseed rape cultivar less susceptible to insect attack but more resistant to fungal disease.

Aphids have already been mentioned as the major temperate agricultural pest. Again, SCR-GC has proved invaluable in identifying semiochemicals having important roles in aphid chemical ecology (Pickett et al. 1992). The aphid sex pheromones have been identified for a mumber of species(Dawson et al. 1990). For the hop aphid(*Phorodon humuli*), an important horticultural crop pest, this comprises a diastereoisomeric pair of a particular type of cyclopentanoid monoterpene (Campbell et al. 1990). The synthetic compounds can be used to attract large numbers of males, which demonstrated for the first time the unequivocal role semiochemicals can play in oriented flight by aphids. A strategy comprising attraction of males to traps containing fungal pathogens and diversion of the spring migrants as they approach their summer host, the hop crop, is being developed for commercial control of this pest. Aphid sex pheromones have also been shown to attract parasitoids (Hardie et al. 1991), targeted for development as biological control agents of aphids within SDDS.

The study of sex pheromone biosynthesis in aphids would prove difficult because of their small size. However, the main part of the pathway exists in certain labiate plants in the *Nepeta* genus. *Nepeta racemosa*(= *mussinii*) produces compounds with exactly the appropriate stereochemistry for the hop aphid sex pheromone (Dawson et al. 1989b, Campbell et al. 1990). Indeed, enzymology studies on this plant have led to successful developments in the molecular biology of enzymes in the early part of the biosynthetic pathway to these compounds (D.L. Hallahan, unpublished data). It is hoped that this work will eventually lead to production of the aphid sex pheromones by fermentor technology, using transgenic organisms. This may, in turn, lead to the production of genetically engineered plants that will themselves interfere with aphid development.

Black bean aphids, *Aphis fabae*, are known to colonise a range of plants but specialize on those in the Leguminosae. To do this they have specially adaped receptors on their antennnae which detect volatile compounds from their host plants. Even ubiquitous plant components such as (Z)-3-hexen-1-yl acetate have very specific receptors which show little response to other closely related compounds. However, in the same region of the antenna are also receptors for volatiles produced by non-host plants, including Compositae (Asteraceae) and Cruciferae (Brassicaceae). Thus, compounds such as 4-pentenyl isothiocyanate, to which the cruciferous feeder *C. assimilis* is strongly attracted, are detected by cells in the antenna of *A. fabae* (Pickett et al. 1993). For the aphid, the isothiocyanate causes repulsion and also avoidance of those chemicals derived from its host (Nottingham et al. 1991). Thus, there is a potential for repellants in use of these anti-host plant chemicals, or kairomone inhibitors.

Plant molecular biology will play an increasingly important role in pest control in the future, particularly in providing more resistant crop plants for SDDS. Another exciting new development is the discovery of wounding signals that can be transmitted between plants, e.g. the volatile fatty acid metabolite methyl jasmonate which has been shown to induce protease inhibitor defence in leaves (Farmer & Ryan 1990) and other related interactions (Gundlach et al. 1992, Olias et al. 1992). Although probably not present in sufficient amounts in oilseed rape to elicit such a response, when added artificially to the air above the plants, this compound causes induction of the indolyl glucosinolates, important for disease resistance in this crop (Wallsgrove et al. in preparation). The compounds causing this effect naturally in oilseed rape and other crops would provide a means of switching-on pathways genetically engineered into crop plants, so that a specific semiochemical effect could be promoted when early monitoring systems indicate that best effects would ensue. The signals, including methyl jasmonate, would be simple and benign compounds related to other semiochemicals. Where communication between the same species of plants is involved, these semiochemicals would be termed pheromones or phytopheromones.

CONCLUSIONS

A critical assessment must continually be made of the new approaches discussed here and it should never be assumed that nature is automatically "kinder" than the carefully regulated use of synthetic chemicals. Nonetheless, with new prospects for use of molecular biology and with the acceptance of the need to understand the complete chemical ecology of crop pests, there should be optimism regarding the future of chemically based pest control.

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