Deltamethrin resistance in the codling moth (Lepidoptera: Tortricidae): inheritance and number of genes involved

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The inheritance of deltamethrin resistance in *Cydia pomonella* (L.) has been investigated by crossing a resistant (Rv) and a susceptible (Sv) strain, derived from a population collected in south-eastern France in 1995. Deltamethrin resistance was suspected to be under the control of a *kdr*-type allele and an enhanced mixed-function oxidase (mfo). F₁ and F₂ progenies were therefore tested through dose–response and enzyme assays. Dose–response relationships indicated that resistance was inherited as an autosomal incompletely recessive ($D = -0.199$) character, involving at least two genes. Enzyme measures suggested the contribution of 1.2 genes to the expression of mfo, with incomplete dominance ($D = 0.460$). Our results support the hypothesis of a polygenic response to deltamethrin selection in the Rv strain, including a major *kdr*-type allele with a minor effect of mfos. In the light of these findings, we consider the resistance in codling moth populations in south-eastern France as a product of an adaptive sequential selection process, occurring through the sequential addition of resistance genes.

Keywords: dominance degree, insecticide, polygenic resistance, resistance evolution, resistance mechanisms, selection.

Introduction

The acquisition of insecticide resistance has given one of the best opportunities to assess microevolution processes, partly because the nature of the selective agent is well identified and partly because, in response to this strong selection pressure, evolution is fast. As resistance reflects changes occurring in genotypic architecture of natural populations, a full understanding of the evolution of this phenomenon requires an accurate knowledge of its genetic basis (Roush & Daly, 1990). But, beyond the evolutionary approach, genetic data constitute a necessary tool for investigating the mechanisms of resistance, and for predicting the behaviour of resistance genes, thus leading to a better estimation of resistance risks in populations. This may provide critical information in pesticide resistance management for the implementation of appropriate control decisions (Georghiou & Taylor, 1986). The mode of inheritance of resistance has been well identified in a wide range of insect species such as mosquitoes (Halliday & Georghiou, 1985; Raymond *et al.*, 1987), aphids (Devonshire & Field, 1991) and the

diamondback moth (Tabashnik *et al.*, 1992), but, to date, no data are available regarding the codling moth, *Cydia pomonella* (L.).

Chemical control failures for this species occurred in the early 1990s in orchards of south-eastern Europe (Waldner, 1993). Resistance to deltamethrin in this pest was first documented in 1995 (Bouvier *et al.*, 1995). A study conducted on 14 French populations of codling moth revealed a correlation between resistance to deltamethrin and enhanced activity of mixed-function oxidases (mfos) (Bouvier *et al.*, 1998). More recently, Brun-Barale *et al.* (2000) demonstrated the involvement of a sodium-channel mutation (*kdr*) in deltamethrin resistance in *C. pomonella*. This mutation is known to play a major role in pyrethroid resistance in insects (Williamson *et al.*, 1996). In this study, our aim was to investigate the inheritance of deltamethrin resistance in *C. pomonella*, and its potential consequences in terms of the population genetics in this species. We focused on the two following questions. (i) Which evolutionary scenario may have led to chemical control failure in south-eastern France? (ii) How would the selected resistance genes behave in natural codling moth populations?

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We used classical crosses between field-derived resistant and susceptible strains to evaluate the maternal effects, the degree of dominance, and the number of genes conferring resistance. This study was also expected to improve knowledge on mechanisms of resistance to deltamethrin in *C. pomonella*. Therefore, we propose a method based on measurement of enzymatic activity to determine the mode of inheritance of the enhanced mfo activity character.

Materials and methods

Insect strains

Codling moths were collected from the field in 1995 using corrugated cardboard trapping strips in an apple orchard at Les Vignères (south-eastern France) where deltamethrin failed to control moth populations. The resistant strain (Rv) was derived from this sample of a wild population by selection for the first 10 generations with increasing doses of deltamethrin that induced 50% mortality, followed by a constant selection pressure (2 mg/L of deltamethrin). The progeny of isolated pairs was tested with discriminating doses of chemical in order to determine the parental genotype (Sauphanor *et al.*, 1998b). This procedure allowed the detection of susceptible adult pairs, whose progeny were used to build the susceptible strain (Sv). The two strains were kept by mass rearing on an artificial diet as described by Guennelon *et al.* (1981).

Genetic crosses

Adult codling moth were introduced into plastic cages (8 cm diameter, 5 cm high) with inner walls covered by thin white paper to receive the eggs, and containing sugared water as a food source. Twelve cages containing five pairs of adults were prepared for each cross and placed at 25°C ± 1°C, 40 ± 10% RH and under a 16:8 h (L:D) photoperiod. Larvae were reared in mass conditions identical to those of the parental strains. Virgin adults (less than 4-h-old) of the susceptible and the resistant strains were reciprocally crossed ($Sv_{female(f)} \times Rv_{male(m)}$; $Rv_f \times Sv_m$) to produce the F_1 hybrids. Because there was no evidence for sex-linkage (see Results), F_1 progeny from both reciprocal crosses were pooled and reared to adult stage for backcrossing to parental strains and intercrossing to produce the F_2 progeny. The resulting backcross ($F_1 \times Rv$) and the F_2 progeny were assessed in order to test the hypothesis of monogenic inheritance.

Bioassays

The susceptibility to deltamethrin of the Sv and the Rv strains and their different crosses was tested on newly hatched larvae (0–6-h-old). Fresh solutions of commercial insecticide were prepared in distilled water for each trial. Deltamethrin, or distilled water for the control, was sprayed on the surface of the diet prepared in 20 × 20 × 20 mm cups, using a Burgerjon tower (Burgerjon, 1956) at a dose of 1.7 mg/cm². After air-drying of the diet for 2 h, each larva was deposited on the treated surface. The cups were closed and kept at 25°C ± 1°C, 40 ± 10% RH and under a 16:8 h (L:D) photoperiod. Mortality was recorded 4 days after treatment.

Enzyme assays

Total nonspecific mfo activity of 3-day-old larvae of the Sv and the Rv strains and their different crosses was determined by measuring 7-ethoxycoumarin-O-deethylation (ECOD) activity according to the procedure of De Sousa *et al.* (1995). The larvae were placed individually in wells of black microplates containing 100 µL of 50 mM sodium phosphate buffer (pH 7.2) and 0.4 mM of ethoxycoumarin. The reaction was stopped after 4 h by adding 100 µL of glycine buffer (10⁻⁴ M), pH 10.4/ethanol (v/v). In order to sediment the larvae in the wells, microplates were centrifuged at 2000 g for 30 s prior to and after the incubation of the enzymatic reaction at 30°C. Wells receiving glycine buffer before incubation were used as blanks. Fluorescence was measured using a microplate reader (HTS 7000, Perkin Elmer) with 380 nm excitation, 465 nm emission filters and 50 for gain.

Data analysis

Mortality data from bioassays were corrected by natural control mortality using Abbott's formula (Abbott, 1925). Values of lethal concentration for 50% of individuals (LC₅₀) and of median mfo activity (mma) were calculated using a probit computer program (Raymond, 1985). They were considered significantly different when 95% confidence limits did not overlap. The degrees of dominance (*D*) for both mortality and mfo activity were determined according to the method of Stone (1968) using the pooled data of the reciprocal F_1 crosses:

$$D = (2X_b - X_a - X_c) / (X_a - X_c),$$

where $X_a = \log_{10}(LC_{50})$ or (mma) of the resistant strain, $X_b = \log_{10}(LC_{50})$ or (mma) of the pooled F_1 , and

$X_c = \log_{10}(LC_{50})$ or (mma) of the susceptible strain. $D = 1$ indicates complete dominance, $0 < D < 1$ incomplete dominance, $-1 < D < 0$ incomplete recessivity, and $D = -1$ complete recessivity. Dominance variances were calculated according to Bloch & Wool (1994), where the standard deviation of resistance is given by the reciprocal of the probit regression slope (Finney, 1971):

$$\sigma_D^2 = 4/k[(\sigma_b^2 + (X_b - X_c)^2\sigma_a^2/k) + ((X_b - X_a)^2\sigma_c^2/k)]$$

where $k = (X_a - X_c)^2$. Dominance level of survival at a given insecticide dose (in our case 0.75 g/L, the dose applied under commercial field conditions), referred to as effective dominance (D_{ML}), was calculated according to the formula as cited in Bourguet *et al.* (2000):

$$D_{ML} = (ML_{F1} - ML_{SS}) / (ML_{RR} - ML_{SS}),$$

where $D_{ML} = 0$ indicates complete recessivity, and $D_{ML} = 1$ complete dominance. The minimum number of independently segregating genes (n) contributing to resistance was estimated according to Lande (1981):

$$n = (\mu_2 - \mu_1)^2 / (8 \times \sigma_s^2),$$

where $\mu_1 = \log_{10}(LC_{50})$ of the resistant strain, and $\mu_2 = \log_{10}(LC_{50})$ of the susceptible strain. $\sigma_s^2 = \sigma_{B1}^2 + \sigma_{B2}^2 - [\sigma_{F1}^2 + 0.5\sigma_{Sv}^2 + 0.5\sigma_{Rt}^2]$ (where σ_{B1}^2 , σ_{B2}^2 , σ_{F1}^2 , σ_{S1}^2 and σ_{R1}^2 were the phenotypic variances of the backcrosses, F_1 , Sv , and Rt , respectively. We also used

this method to estimate the number of genes involved in mfo activity. The null hypothesis of monogenic resistance was tested from mortality data of backcross progeny compared to theoretical expectations using the χ^2 -test (Tabashnik *et al.*, 1992).

Results

Inheritance of resistance to deltamethrin

The LC_{50} of the Rv strain was 93.7 times greater than the LC_{50} of the Sv strain (Table 1). The dose-response of parental strains and of their F_1 were characterized by straight lines when bioassayed with deltamethrin, indicating that Sv and Rv strains were homogeneous for susceptibility and resistance to this insecticide, respectively (Fig. 1). The LC_{50} values of the reciprocal F_1 crosses between the susceptible and the resistant strains did not differ significantly (Table 1). The null hypothesis of the parallelism test between the two probit regression lines of the reciprocal F_1 was not rejected at the 5% significance level ($\chi^2 = 1.59$, d.f. = 8, $P = 0.99$). This equality suggested that sex linkage of resistance did not occur and that the genetic basis of the deltamethrin resistance was autosomal inheritance. Data of the reciprocal F_1 hybrids were combined. The degree of dominance of the Rv response to deltamethrin (D) based on the LC_{50} data was -0.199 ± 0.039 , indicating an incompletely recessive resistance. The effective dominance, $D_{ML} = 0.480$, defined as the mortality of heterozygotes relative to that of both homozygotes at a given insecticide concentration applied in the field

Table 1 Response to deltamethrin of first instar codling moth for a homozygous deltamethrin-resistant strain (Rv), a susceptible strain (Sv) and various crosses

Strain or cross	n	Control mortality (%)	LC_{50} (mg L ⁻¹)	(95% CL)	LC_{90} (mg L ⁻¹)	(95% CL)	Slope $\pm$ SE	HF*	LC_{50} ratio†
Sv	903	6.5	0.031	(0.026–0.036)	0.134	(0.109–0.172)	2.01 ± 0.13	1.96	1
Rv	1000	7.7	2.905	(2.432–3.429)	16.845	(13.417–22.242)	1.67 ± 0.11	1.88	93.7
F_1									
$Sv_f \times Rv_m$	670	4.2	0.177	(0.147–0.209)	0.849	(0.667–0.158)	1.88 ± 0.15	1.67	5.7
$Rv_f \times Sv_m$	439	0.0	0.214	(0.171–0.264)	1.247	(0.916–1.894)	1.67 ± 0.15	2.15	6.9
$F_{1\ddagger}$	1109	2.7	0.190	(0.166–0.218)	1.012	(0.830–1.288)	1.76 ± 0.10	0.73	6.1
$F_{2§}$	1110	4.3	0.088	(0.072–0.107)	0.805	(0.616–1.117)	1.33 ± 0.08	0.74	2.8
Backcross									
$F_1 \times Sv¶$	830	4.6	0.054	(0.044–0.066)	0.359	(0.272–0.509)	1.55 ± 0.11	2.05	1.7
$F_1 \times Rv**$	670	3.3	0.557	(0.438–0.690)	3.829	(2.904–5.426)	1.53 ± 0.12	0.90	17.9

*HF, the heterogeneity factor, is equal to χ^2 divided by d.f.

† LC_{50} of Rv and crosses divided by the LC_{50} of the Sv strain.

‡Combined data from the two reciprocal crosses.

§($Rv_{male(m)} \times Sv_{female(f)}$) and ($Sv_m \times Rv_f$) pooled.

¶(Pooled $F_{1m} \times Sv_f$) and ($Sv_m \times$ pooled F_{1f}) combined. The pooled F_1 corresponds to a combined reciprocal F_1 hybrid.

** (Pooled $F_{1m} \times Rv_f$) and ($Rv_m \times$ pooled F_{1f}) combined.

Fig. 1 Responses of *Cydia pomonella* to deltamethrin. For each dose, the response is presented in terms of the percentage mortality observed in the susceptible (Sv) and the resistant (Rv) parental strain, in their pooled F₁ and the backcross (F₁ × Rv), as well as the percentage mortality expected for the backcross with the resistant parental strain calculated by assuming monogenic inheritance.

(Bourguet *et al.*, 2000), indicates a codominant resistance. Observed mortalities of the backcross progeny with the resistant parent (Fig. 1) differed significantly from the expected theoretical curve based on the hypothesis of single factor resistance ($\chi^2 = 46.54$, d.f. = 5, $P = 0.00$). We obtained similar results (Fig. 2) when the test of a monogenic model was performed on the F₂ progeny ($\chi^2 = 95.88$, d.f. = 8, $P = 0.00$). Deviations from expected mortality in the backcross and the F₂ experiments suggested that more than one gene controlled the resistance to deltamethrin in the Rv strain. Using Lande's method (Lande, 1981) and the data on parental strains and reciprocal F₁, it was estimated that a minimum number of 2.2 genes are involved in deltamethrin resistance.

Inheritance of the mfo activity involved in deltamethrin resistance

Inheritance patterns of mfo activity were assessed from the same crosses as those used for studying deltamethrin resistance (Table 2). The mean activity level for the Rv strain was five-fold higher than that of the Sv strain and this difference was statistically significant at the 5% significance level (ANOVA: $F = 88.679$, $P = 0.0001$). The degree of dominance estimated using the median mfo activities (D) was 0.460. This result indicated an incomplete dominance for the mfo activity, which was controlled by 1.2 genes.

Fig. 2 Responses of *Cydia pomonella* to deltamethrin. For each dose, the response is presented in terms of the percentage mortality observed in the susceptible (Sv) and the resistant (Rv) parental strain, in the F₂, as well as the percentage mortality expected in the F₂ calculated by assuming monogenic inheritance.

Table 2 Monooxygenase activity (ECOD) (measured in pg of 7OH formed/larva/min) in the parental strains (Sv and Rv) of the codling moth and various crosses involving these strains

Strain	n	Mean activity	Range of activity
Sv	48	17.24	1.15–44.83
Rv	46	92.03	18.54–213.90
F ₁ *	51	58.48	3.58–216.02
F ₂ †	44	49.80	5.95–171.22
Backcross			
F ₁ × Sv‡	47	32.27	0.00–150.43
F ₁ × Rv§	49	68.35	5.95–163.06

*Combined data from the two reciprocal crosses.

†(Rv_{male(m)} × Sv_{female(f)}) and (Sv_m × Rv_f) pooled.

‡(Pooled F_{1m} × Sv_f) and (Sv_m × pooled F_{1f}) combined.

§(Pooled F₁ corresponds to a combined reciprocal F₁ hybrid.

§(Pooled F_{1m} × Rv_f) and (Rv_m × pooled F_{1f}) combined.

Discussion

Inheritance of deltamethrin resistance

Our results indicated that resistance to deltamethrin in the Rv laboratory strain appeared to be controlled by at least two factors. Previous results obtained in the laboratory support the idea that several genes are involved in Rv resistance to deltamethrin. First, the involvement of enhanced mfo activity in the resistance of the Rv strain to deltamethrin was demonstrated by synergism assays with specific inhibitors and by *in vivo* metabolism of [¹⁴C] deltamethrin (Sauphanor *et al.*, 1997). Second, we recently established the presence of a *kdr* mutation in the sequence of one voltage-dependent sodium-channel gene of Rv, i.e. leucine to phenylalanine replacement in the transmembrane segment IIS at position 1014 (Brun-Barale *et al.*, 2000). A diflubenzuron-selected strain displaying comparable mfo activity to that found in the Rv strain (Sauphanor *et al.*, 1997), but lacking the *kdr* mutation (Brun-Barale *et al.*, 2000), exhibited a 6.2-fold resistance to deltamethrin (Sauphanor *et al.*, 1998a). The additional effect of the *kdr* mutation in the Rv strain increased the resistance to deltamethrin to 93.7-fold suggesting that the *kdr* gene is the main mechanism of the resistance to deltamethrin in the Rv strain. Our results also show that deltamethrin resistance in the Rv strain was expressed as an incompletely recessive trait ($D = -0.199$). Consequently, given that the mfo gene was incompletely dominantly inherited, we can assert that the major deltamethrin resistance factor in the Rv strain is incompletely recessive. The *kdr*-type resistance allele has already been shown to be incompletely recessive (Plapp, 1976; Halliday & Georgiou, 1985) and inheritance of synthetic pyreth-

roid mfo-type resistance has also previously been found to be monogenic with incomplete dominance in *Helioverpa armigera* (H.) (Daly & Fisk, 1992), as was the case in our Rv strain. Our results, i.e. the additional effect of *kdr* and mfo, are in agreement with several genetic studies showing the involvement of these two mechanisms in pyrethroid resistance (Roush *et al.*, 1986; McDonald & Schmidt, 1987; Payne *et al.*, 1988).

The occurrence of a segregation plateau at 60% mortality, rather than 50%, in the expected results of the F₁ × Rv backcross indicated that the (RR/RS) ratio was different from 1:1. According to Payne *et al.* (1988), divergence from a 1:1 segregation model may be due to the fact that: (i) interactions of the RR genome with an unlinked gene from the susceptible genetic background are lethal for a portion of the RR genotype, or (ii) resistance is not expressed in a portion of the RR genotype. However, we did not formally test these hypotheses in the present study.

Pathway of acquisition of deltamethrin resistance in *Cydia pomonella* (L.)

Adaptation of insect populations to chemical treatments is generally assumed to occur through a single-gene response (McNair, 1991; McKenzie & Batterham, 1994). Because the doses applied in the field are designed to kill all individuals, selection is expected to act outside the original viability distribution of the population and to retain only single-locus alleles conferring high resistance levels. Hence, phenotypic variants carrying rare mutations conferring resistance to insecticide concentrations above those that eliminate 100% of the initial susceptible population have a selective advantage. This may clarify why monogenic responses to selection for insecticide resistance are common, although not universal (Roush & McKenzie, 1987; Scott *et al.*, 2000). However, resistance occurring in natural populations is often shown to imply several loci, but at an extremely limited number (Roush & Daly, 1990). A shift from monofactoriality to multifactoriality may be associated with a subsequent addition of genes, as a consequence of an adaptive sequential selection process. Chlorpyrifos resistance in *Culex pipiens* (L.) provides an example of such an evolutionary scenario (Raymond *et al.*, 1987). In this species, resistance was initially controlled by a single gene encoding detoxifying esterases, but has later included an altered acetylcholinesterase and enhanced mfos.

Acquisition of pyrethroid resistance in the codling moth may have followed an identical evolutionary pathway. At the early stages of chemical control of codling moth in south-eastern France, organophosphates were usually spread in apple orchards

(Audemard, 1963). The use of several compounds related to this chemical group may be responsible for selection for a nonspecific detoxifying resistance mechanism, such as mfos, and conferring cross-resistance to pyrethroids. Selection of additional *kdr*-alleles by subsequent deltamethrin applications further weakened the effectiveness of pyrethroids through a higher combined resistance factor.

Expected consequences for the rate of evolution of resistance

The sequential acquisition of deltamethrin resistance may, in theory, influence the rate at which resistance evolves in codling moth populations. It is generally assumed that monogenic resistance is more likely to spread than is polygenic resistance. This has been supported by Hoy *et al.* (1980) and Roush & Hoy (1981) for pyrethroid and carbaryl-resistant *Metaseius occidentalis* (N.) strains, showing that the mode of inheritance of pesticide resistance – polygenic *vs.* monogenic – can influence the rate of evolution of resistance frequency. This trend may be particularly pronounced if treatments are temporarily relaxed for a few generations or spatially alternated in mosaic structures, as dilution of resistance alleles occurs as a consequence of hybridization of polygenically resistant genotypes with susceptible genotypes (Roush & McKenzie, 1987). The resulting phenotypes would not be sufficiently resistant to survive subsequent pesticide applications, especially if the major gene controlling resistance is expressed recessively; another factor contributing to the spread of resistance being the dominance of resistance alleles (Georghiou & Taylor, 1986). However, it is critical to note that dominance is not an intrinsic property of an allele (Sved & Mayo, 1970). Its expression typically depends on the chemical and on the dose applied, leading to the concept of effective dominance (D_{ML}) (Bourguet *et al.*, 2000). If the dose applied in the field is high enough to kill heterozygous individuals, a dominant trait of resistance (as defined as the position of the mortality curve of heterozygotes relative to that of both homozygotes) turns into a functionally recessive character, as first underlined by Curtis *et al.* (1978). In the present work, estimation of both dominance and effective dominance indicated that deltamethrin resistance was incompletely recessive (–0.199) and codominant (0.480), respectively. However, D_{ML} predictions based on extrapolation of laboratory data to field conditions must be carefully considered with regard to their utilization in pest management strategies for two main reasons. Firstly, the range of concentrations that establishes dominance may differ between laboratory and field populations (Roush & Daly, 1990) as a

consequence of variability of mortality curves of the three genotypes between laboratory and field conditions. Secondly, because the effectiveness of residual applications is expected to decline due to chemical degradation during the control period, the resistance level expressed in heterozygotes could then remain high enough to allow survival. For example, the *kdr* mutation became fully dominant in expression under low pyrethroid concentrations in houseflies (Denholm *et al.*, 1990). In south-eastern France, deltamethrin is still efficient on benzoylurea-resistant codling moth field populations, in which mfos displaying the same activity as our F₁ had been selected (Sauphanor *et al.*, 1998a). Moreover, deltamethrin recommendations include an overkill factor which ensures population control even under variations between the dose applied and the dose received by the insect (probit analysis provided by laboratory experiments showed that the dose applied in the field induced 70–80% mortality for homozygous resistant individuals). According to these data, we believe that the *kdr*-type allele may be expressed in the field as a recessive trait. Assuming that the determinism of resistance to pyrethroids in field populations and in our laboratory Rv strain is similar, one would thus expect that pyrethroid resistance development may be theoretically delayed under appropriate control strategies that would favour dilution of resistance alleles by enhanced flow of susceptible alleles and by periodic relaxation of selection pressure.

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