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The molecular basis of dominance relationships: the case of some recent adaptive genes

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Abstract

A controversial debate in evolutionary biology has been to explain why deleteri ous mutations are usually recessive to their wild-type allele. For Fisher, dominanc of the wild-type is the result of selection, whereas for Wright it is a mer consequence of the biochemical properties of physiological pathways. Over time Wright's theory has appeared as the most appropriate, and Kacser and Burn explained why the widespread occurrence of recessive mutants is the inevitabl consequence of the kinetic structure of enzyme networks. Does Wright and Kacse and Burns (W-K-B)'s theory apply for newly arisen adaptive genes? A survey o more than 70 studies shows that pesticide resistance conferred by mutation decreasing the affinity of the pesticide target-sites varies from complete recessivit to complete dominance. This review shows that dominance always has a purel physiological explanation that can be roughly, but not simply, predicted b W-K-B's theory. Thus, although W-K-B's theory remains powerful for predictin the recessivity of deleterious mutations involved in enzymatic pathways, no genera theory emerges from the study of other situations, and molecular explanations ar to be sought on a case by case basis.

Introduction

Studies of mutagenesis in many organisms indicate that over 90% of leth mutations are recessive to wild-type (Simmons and Crow, 1977; Wilkie, 1994) an

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two main theories have been offered to explain this general pattern. Fisher (se Fisher, 1958; Sved and Mayo, 1970) believed that the recessivity of recurren deleterious mutations is the end-product of natural selection. He suggested tha most of these mutations were originally co-dominant and became progressivel recessive through the accumulation of modifier alleles at other loci. Wright (se Wright, 1977; Sved and Mayo, 1970) proposed that dominance of the wild-typ allele is a mere consequence of metabolism, assuming that most deleterious muta tions cause a reduction in enzymatic activity. Thus, if the wild-type allele is mor active than necessary, then the rate of reaction is likely to be substrate rather tha enzyme limiting. Consequently, a deleterious allele that greatly reduces enzym activity should appear recessive or nearly recessive. Kacser and Burns (1981) gav a modern analysis of Wright's theory (see Keightley, 1996) and they detailed wh a change in enzyme concentration or activity at any one of a step of a metaboli pathway is unlikely to have a large effect on the output of the system. They claime (p. 640) that "*the recessivity of mutants is an inevitable consequence of the kineti properties of enzyme-catalyzed pathway and [. . .] no other explanation is required*"

Testing Fisher's or Wright's theories has proved a difficult task. Charlesworth (1979) observed an inverse correlation between the homozygous effect of a muta tion on fitness (s) and its dominance level (h), whereas no such correlation can b predicted from Fisher's theory. Orr (1991) analyzed the dominance levels o mutations in the haploid alga *Chlamydomonas reinhartii*. This alga possesses som short diploid states allowing the estimation of the dominance level of mutations Orr found that mutations are recessive just as among diploid species. These result give support to Wright's theory of dominance and its detailed explanation b Kacser and Burns (1981) had a wide range of applications (e.g., Turelli and Orr 1995). However, this theory has important restrictions (see Sved and Mayo, 197(Wright, 1977; Charlesworth, 1979; Kacser and Burns, 1981; Keightly and Kacser 1987; Orr, 1991; Mayo and Bürger, 1996). First, the gene considered must code a enzyme or a quasicatalytic product (Kacser and Burns, 1981, p. 663). Second, thi enzyme must operate in a substrate limiting context, so that a decrease in activit does not affect the end product(s) of the reaction. Third, the phenotype studie must be monotonically related to the end product(s) of the reaction. As a conse quence, Kacser and Burns (1981) have emphasized (p. 664) that the class c non-catalytic gene products "*must remain outside our framework, until more investi gations reveal the precise mechanism of their involvement*".

To better understand how dominance is determined, Hodgkin (1993) and Wilki (1994) have investigated the molecular basis of dominant lethal mutations in huma disorders. Some correspond to a *loss of function, i.e.* quantitatively altered function which are critical rate limiting steps within a metabolic pathway and are sensitiv to reduced enzyme activity. Others represent a *gain of function, i.e.*, qualitativel altered functions which are sufficient to cause human diseases in the heterozygou state. Hodgkin (1993) concluded that the dominance of new mutations is ofte unpredictable.

Pesticide resistance is a suitable model to further investigate dominance relation ships (Bourguet et al., 1996a): most genes and mutations responsible for suc

resistance have been identified, and the physiological processes in which they ar involved are known. In this paper, we present an extensive survey of the dominanc of pesticide resistance due to target-site modifications, and we suggest molecula and physiological explanations for the observed pattern.

Methods

Targets

Pesticide resistance can occur as the result of behavioral avoidance, reduce penetration, increased detoxification or excretion, or target-site modification (e.g. Mullin and Scott, 1992). This latter mechanism is of particular interest fo dominance investigations as targets are encoded by single genes with two alleles: S corresponding to the wild-type sensitive target and R to the mutant insensitiv target. We selected studies describing monofactorial pesticide resistance conferre by six classes of pesticide target-sites displaying R alleles: three enzymes (acetyl cholinesterase, acetolactate synthase and vitamin K2,3-epoxide reductase) and thre channels or receptors (sodium and chloride channels, and δ-endotoxin receptors) Each target is briefly described:

Acetylcholinesterase

Acetylcholinesterase (AChE; acetylcholine acetylhydrolase, EC 3.1.1.7) is a ke enzyme of the central nervous system of insects where it degrades the synaps neurotransmitter acetylcholine (ACh) (see Toutant, 1989, for review). This enzym is inhibited by organophosphorous and carbamate insecticides, and insensitiv AChE is due to single or combination of point mutations (e.g., Mutero et al., 1994 Insensitive AChE have been reported in more than 25 insect species (Fournier an Mutéro, 1994).

KO reductase

A second example is a pesticide target-site involved in an enzyme cascad Vitamin K2,3-epoxide reductase (KO reductase) is one of the numerous enzyme involved in the coagulation process of mammalian blood. It both reduces vitami K in its hydroquinone form (an essential co-factor for blood clotting) and recycle vitamin K. Warfarin is an anticoagulant drug used to control populations of som pest mammals. This pesticide binds irreversibly KO reductase interrupting th vitamin K recycling (Bell and Matschiner, 1972). In Norway rats *Rattus norvegicu* the extensive use of this drug has resulted in the selection of two distinct modifie targets (see Thijssen, 1995 for review).

Acetolactate synthase

The acetohydroxy acid synthase (AHAS, EC 4.1.3.18), generally known a acetolactate synthase (ALS), catalyzes two reactions, the condensation of tw pyruvate molecules to yield acetolactate, and the condensation of pyruvate an

ketobutyrate to yield acetohydroxybutyrate. This is the first enzyme in the biosyn thetic pathway leading to the production of isoleucine, leucine and valine in plant and microorganisms. This enzyme is the target site of four families of herbicides the sulfonylurea, imidazolinone, triazolopyrimidine and pyrimidinyl oxybenzoat herbicides. Mutations resulting in resistance to these herbicides, have been shown t be mostly due to single or combination of base pair mutations in gene coding th ALS catalytic subunit (e.g., Yadav et al., 1986; Haughn et al., 1988; Bernasconi e al., 1995).

Sodium channels

The voltage-dependent sodium channel (Na^+Vdp) generates nerve action poten tials (Narahashi, 1992). Binding of DDT and pyrethroid insecticides to this protei leaves the sodium channels irreversibly open. A resistance mechanism, name knockdown resistance (*kdr*), is provided by target-modification due to mutation(s associated with one of the sodium channel genes (Amichot et al., 1992; Knipple e al., 1994; Williamson et al., 1996).

Chloride channels

These chloride channels are receptors of GABA (γ-aminobutyric acid), a majo neurotransmitter in vertebrates and invertebrates. Resistance to cyclodiene insecti cides appears to be conferred by replacement of a single amino acid (ffrench-Con stant et al., 1993a) by either a serine or a glycine residue (ffrench-Constant et al. 1993b). Replacements of this same amino acid are found in cyclodiene resistanc strains of house flies, red flour beetles, cockroaches (Thompson et al., 1993a) yellow fever mosquitoes (Thompson et al., 1993b) and whiteflies (Anthony et al. 1995).

δ-endotoxin receptors

These midgut glycoprotein receptors are the targets of *Bacillus thuringiensi* insecticidal crystal proteins. Upon ingestion by insects, the crystal dissolves in th midgut lumen and is proteolytically activated to a toxic fragment that binds t receptors. Subsequently, this δ-endotoxin, or parts thereof, appears to insert in th membrane and to form pores permeable to small ions and molecules. These pore will enlarge from osmotic swelling, and eventually cell lysis will occur (see Gill e al., 1992 for review). Resistance to *Bacillus thuringiensis* have been reviewed (e.g McGaughey and Whalon, 1992; Tabashnik, 1994; Ferre et al., 1995).

Dominance level

Dominance, rather than an intrinsic property of a gene, describes the relationshi between the phenotypes of three genotypes (Sved and Mayo, 1970). Therefore dominance depends on the character under consideration and may vary from on character to another. In this paper, the phenotypic character studied is "pesticid tolerance".

For resistance conferred by insensitivity to acetylcholinesterase, channels or receptors, pesticide tolerance are estimated by the LC_{50}, *i.e.* the pesticide concentration giving 50% mortality. In the literature, dominance is usually calculated using Falconer's formula (1964) according to Stone (1968b): $D = [2LC_{50}(RS) - LC_{50}(RR) - LC_{50}(SS)]/[LC_{50}(RR) - LC_{50}(SS)]$, where RR, RS and SS represent the homozygous resistant, heterozygous, and homozygous susceptible genotypes and where LC_{50} values are expressed in logarithms. In this case D varies from -1 (complete recessivity) to 1 (complete dominance). However, to obtain a more classical 0–1 range, in this review, dominance was calculated as $D = [LC_{50}(RS) - LC_{50}(SS)]/[LC_{50}(RR) - LC_{50}(SS)]$ (Bourguet et al., 1996a, Bourguet et al., 1997). Thus when RS and RR genotypes have the same LC_{50}, then $D = 1$ and R is dominant to S. When RS and SS have the same LC_{50}, then $D = 0$ and R is recessive to S. Finally, when RS has an intermediate LC_{50}, $D = 0.5$ and alleles R and S are co-dominant. Five categories were defined according to Georghiou (1969): (1) Recessive when $D \approx 0$; (2) Semi-recessive when $0 < D < 0.5$; (3) Co-dominant when $D \approx 0.5$; (4) Semi-dominant when or $0.5 < D < 1$ and (5) Dominant when $D \approx 1$.

For pesticide resistance conferred by acetolactate synthase and vitamin K2,3-epoxide reductase insensitivity, LC_{50} data were not available. Tests for herbicide resistance provided by acetolactate synthase modifications involved a post-emergence treatment by a discriminative dose of pesticide (*i.e.* a dose that kills all SS genotypes). Plants showing normal growth of both the shoot and the root apical meristems, several days after treatment, are scored as resistant (see Haughn and Somerville, 1986). For warfarin resistance due to vitamin K2,3-epoxide reductase insensitivity, resistance of rats *Rattus norvegicus* were screened at the age of 4 months by feeding them for 6 days on medium oatmeal containing 0.005% warfarin. Mortality was recorded over a 28-day period (see Greaves and Ayres 1977). Dominance of alleles R of these two target-sites is estimated by comparing the survival of the three genotypes. When RS and RR genotypes have the same mortality level, then R is dominant. When RS and SS genotypes have the same mortality level, then R is recessive. Finally, when RS have intermediate mortality level, R and S are co-dominant.

Predictions

For some pesticide concentrations, the sensitive enzyme is partly or completely inhibited while insensitive enzymes are unaffected, so that alleles S and R may be considered as deleterious and wild type, respectively. Therefore, dominance of allele S should be predicted using the equations of Kacser and Burns (1981) by defining the ratio of enzyme activities, e:

$$e = \frac{E_{SS}}{E_{RR}}$$

where E_{SS} and E_{RR} are the activity of SS and RR homozygotes respectively Following, equation 6 (page 654) of Kacser and Burns (1981), the cominance level D, is given by

$$D = \frac{Z_j(1-e)+e}{Z_j(1-e)+1}$$

where Z_j corresponds to the extent to which the enzyme j "controls" a particulai flux with

$$\sum_{i=1}^{n} Z_i = 1$$

where n is the number of enzymes on the flux response. When sensitive enzymes ar fully inhibited (i.e. when $E_{SS} \approx 0$), then $e = 0$ and

$$D \approx \frac{Z}{Z+1}$$

Both ALS and KO reductase are involved in cascade enzymatic pathways wher n is large so that Z is probably close to 0 (see Kacser and Burns, 1981, p. 648 fo further explanations), so that the predicted value is therefore $D \approx 0$. Thus resistanc by modifications of ALS or KO reductase enzymes is predicted to be dominant

AChE is involved in a restricted pathway, but no estimates of its Z value ar available. As Z varies between 0 and 1, D varies between 0 and 0.5. Thus resistanc by modification of an AChE target is predicted to be co-dominant to dominan according to Wright and Kacser and Burns (W-K-B)'s theory of dominance. N prediction according to Kacser and Burns (1981) are available for non-enzymati targets such as ionic channels or δ-endotoxin receptor.

Results

A survey of more than 70 studies (Tab. 1) shows that pesticide resistanc provided by target-site mutations varies from complete recessivity to complet dominance. For enzymatic targets, resistance varied from semi-recessivity to com plete dominance. For ion channel and receptor targets, resistance varied betwee co-dominance and recessivity in some cases and semi-recessivity to dominance i others. We suggest below that these patterns can largely be explained by th physiological and molecular mechanisms of each target-site.

Enzymes

Acetylcholinesterase

Resistance conferred by insensitive AChEs is generally semi-dominant and varie from semi-recessivity to dominance (Tab. 1). The incomplete dominance level i

explained by the relationship between survival and AChE activity, the latter being related to AChE amount (Hoffmann et al., 1992). Thus, because heterozygous RS possess only half the quantity of insensitive AChE present in homozygous RR, they display a lower tolerance and resistance appears as semi-dominant (Fournier and Mutero, 1994). Furthermore, AChE activity is often altered with resistance (see Fournier and Mutero 1994 for review) so that in heterozygotes, the 50% insensitive AChE (remaining uninhibited) account for less than 50% of the total AChE activity. The consequence is a marked decrease in survivorship and hence a reduced level of dominance. This may explain the recessive resistance for propoxur found in a strain of *Culex pipiens* (Tab. 1) where the activity of the insensitive AChE is only one-fourth that of the wild-type enzyme (Raymond et al., 1986; Bourguet et al. 1997a).

The complete dominance for propoxur resistance found in another strain of *Culex pipiens* (Bourguet et al., 1997a) is explained by the interaction of a second enzyme target, the choline acetyltransferase (ChAT, EC 2.3.1.6) (Bourguet et al. 1997b). In this strain the modified AChE is more than 300 000 fold less sensitive to the propoxur (Raymond et al., 1986; Bourguet et al., 1996b). As a consequence, at high propoxur concentrations, mortality of RR and RS individuals is due to the inhibition of the ChAT instead of the AChE (Bourguet et al., 1997b). Because the ChAT enzyme is probably unmodified in susceptible and resistance strains, RS and RR present the same propoxur mortality curves and R appears as fully dominant.

KO reductase

Two distinct modified targets have been selected in the Norway rat. One has a reduced sensitivity to warfarin (Hildebrandt and Suttie, 1982) and provides fully dominant resistance (Greaves and Ayres, 1967, Tab. 1). This indicates that half KO reductase activity is sufficient to ensure a normal life. The second modified target has a normal sensitivity to warfarin (McNicoll, 1986) but an increased reactivation (Thijssen, 1987) generating sufficient free and active enzyme to meet the demand. The resistance provided by this second modified target is semi-dominant (Greaves and Ayres, 1976; Greaves and Ayres, 1977, Tab. 1). Because this insensitive KO reductase has a normal sensitivity to pesticide, its activity is lower in the presence of warfarin. For some heterozygous rats, this reduced activity coupled with the inhibition of the 50% of sensitive KO reductase decrease the activity below the threshold compatible with life and resistance appears as semi-dominant.

Acetolactate synthase

Resistance is found dominant for several R alleles in different plant species (Tab. 1). However, numerous mutations conferred a semi-dominant resistance (Tab. 1). The same explanation given for semi-dominant resistance conferred by insensitive AChE may apply. In *Escherichia coli* and *Saccaromyces cerevisiae* the amino acid substitution producing an ALS less sensitive to herbicide inhibition also reduced considerably its catalytic activity (Falco and Dumas, 1985; Yadav et al., 1986). In heterozygotes submitted to herbicides, the inhibition of sensitive ALS target associated with a strong reduced activity of insensitive ALS results in a drasti

Table 1. Dominance levels of resistances conferred by different insensitive pesticide target-sites.

Pesticide targets	Pesticides	Dominance[a]	Species	References
Enzymes				
AChE	methyl parathion	1.16	*Heliothis virescens*	Gilbert et al. (1996)
	carbaryl	1.06	*Nephotettix cincticeps*	Hama and Iwata (1978)
	fenthion	1.01 – 0.92	*Boophilus microplus*	Stone et al. (1976)
	propoxur	1.00	*Culex pipiens* complex	Bourguet et al. (1997a)
	parathion	0.99	*Tetranychus urticae*	Ballantyne nad Harrison (1967)
	parathion	0.91	*Tetranychus urticae*	Schulten (1968) in Smissaert et al. (1975)
	dioxathion	0.88	*Boophilus microplus*	Stone (1968b)
	malathion	0.88 – 0.87	*Culex tritaeniorhynchus*	Takahashi and Yasumoti (1987)
	bromophos ethyl	0.87	*Boophilus microplus*	Stone et al. (1976)
	fenthion	0.86–0.84	*Boophilus microplus*	Stone et al. (1976)
	tsumacide	0.84	*Nephotettix cincticeps*	Hama and Iwata (1978)
	demethon-S-methyl	0.84	*Tetranychus urticae*	Schulten (1968) in Smissaert et al. (1975)
	carbofuran	0.84 – 0.78	*Lepinotarsa decemlineata*	Ioannidis et al. (1992)
	carbofuran	0.83 - 0.76	*Lepinotarsa decemlineata*	Ioannidis et al. (1992)
	diazinon	0.81	*Boophilus microplus*	Wilson et al. (1971)
	formothion	0.81 – 0.76	*Boophilus microplus*	Stone (1968b)
	propoxur	0.79	*Nephotettix cincticeps*	Hama and Iwata (1978)
	azinphosmethyl	0.77	*Tetranychus urticae*	Schulten (1968) in Smissaert et al. (1975)
	diazinon	0.75 – 0.74	*Boophilus microplus*	Wilson et al. (1971)
	demethon-S-methyl	0.65	*Tetranychus urticae*	Schulten (1966)
	chlorpyrifos	0.61	*Culex pipiens* complex	Raymond et al. (1987)
	propoxur	0.21	*Culex pipiens* complex	Bourguet et al. (1997a)
	propoxur	0.16	*Culex pipiens* complex	Bourguet et al. (1997a)
ALS	imazapyr	dominant	*Arabidopsis thaliana*	Haughn and Somerville (1990)
	chlorsulfuron	dominant	*Arabidopsis thaliana*	Haughn and Somerville (1986)
	chlorsulfuron	dominant	*Nicotiana tabacum*	Chaleff and Ray (1984)
	sulfometuron methyl	dominant	*Nicotiana tabacum*	Chaleff and Ray (1984)
	sulfometuron methyl	dominant	*Saccharomyces cerevisiae*	Falco and Dumas (1985)
	sulfometuron methyl	semi-dominant	*Nicotiana tabacum*	Chaleff and Ray (1984)
	sulfometuron methyl	semi-dominant	*Saccharomyces cerevisiae*	Falco and Dumas (1985)
	chlorsulfuron	semi-dominant	*Nicotiana tabacum*	Chaleff and Ray (1984)

Table 1. (continued).

Pesticide targets	Pesticides	Dominance[a]	Species	References
KO reductase	warfarin	dominant	*Rattus norvegicus*	Greaves and Ayres (1967)
	warfarin	semi-dominant	*Rattus norvegicus*	Greaves and Ayres (1976, 1977)
Channels and receptors				
Sodium channel	permethrin	0.51	*Haematobia irritans*	Roush et al. (1986)
	bioresmethrin	0.50	*Aedes aegypti*	Malcolm and Wood (1982)
	permethrin	0.41	*Culex pipiens* complex	Halliday and Georghiou (1985)
	permethrin	0.41 – 0.40	*Aedes aegypti*	Malcolm and Wood (1982)
	permethrin	0.40	*Heliothis virescens*	Payne et al. (1988)
	DDT	0.36	*Boophilus microplus*	Stone (1962a)
	DDT	0.31	*Culex pipiens* complex	Halliday and Georghiou (1985)
	permethrin	0.29	*Leptinotarsa decemlineata*	Argentine et al. (1989)
	permethrin	0.29 – 0.27	*Haematobia irritans*	McDonald and Schmidt (1987)
	cypermethrin	0.28	*Haematobia irritans*	Roush et al. (1986)
	permethrin	0.27	*Heliothis virescens*	Payne et al. (1988)
	DDT	0.25	*Blatella germanica*	Cochran and Ross (1962)
	DDT	0.24 – 0.17	*Boophilus microplus*	Stone (1962a)
	DDT	0.19 – 0.17	*Musca domestica*	Hoyer and Plapp (1971)
	DDT	0.17	*Culex tarsalis*	Plapp and Hoyer (1968)
	DDT	0.04	*Musca domestica*	Busvine (1953)
GABA receptor	dieldrin	1.14 – 1.09	*Boophilus microplus*	Stone (1962b)
	dieldrin	1.11	*Boophilus microplus*	Stone (1962b)
	dieldrin	0.83 – 0.82	*Anopheles gambiae*	Davidson (1956)
	γ-BHC	0.74	*Rhipicephalus appendiculatus*	Lourens (1980)
	dieldrin	0.65	*Culex pipiens* complex	Tadano and Brown (1961)
	dieldrin	0.65	*Aedes aegypti*	Khan and Brown (1961)
	lindane	0.64	*Tribolium castaneum*	Beeman and Stuart (1990)
	dieldrin	0.64 – 0.48	*Musca domestica*	Milani (1963)
	γ-BHC	0.61	*Anopheles gambiae*	Davidson (1956)
	endrin	0.58	*Gambusia affinis*	Yarbrough et al. (1986)
	dieldrin	0.57	*Musca domestica*	Guneidy and Busvine (1964)
	dieldrin	0.56	*Culex pipiens* complex	Pennel and Hoskins (1964)
	dieldrin	0.48	*Drosophila melanogaster*	ffrench-Constant and Roush (1991)
	dieldrin	0.37	*Culex pipiens* complex	Tadano and Brown (1961)

Table 1. (continued).

Pesticide targets	Pesticides	Dominance[a]	Species	References
δ-endotoxin receptor	CryIA(b)	0.49 – 0.02	*Plutella xylostella*	Martinez-Ramirez et al. (1995)
	Dipel	0.47	*Plodia interpunctella*	McGaughey and Beeman (1988)
	Dipel	0.44	*Plodia interpunctella*	McGaughey and Beeman (1988)
	Dipel	0.41	*Plodia interpunctella*	McGaughey and Beeman (1988)
	Dipel	0.37	*Plodia interpunctella*	McGaughey and Beeman (1988)
	Dipel	0.33	*Plodia interpunctella*	McGaughey and Beeman (1988)
	CryIA(b)	0.19	*Heliothis virescens*	Gould et al. (1995)
	Dipel	0.16 – 0.05	*Plodia interpunctella*	McGaughey (1985)
	Dipel	0.09	*Plutella xylostella*	Tabashnik et al. (1992);

[a] When LC_{50} of both crosses (females RR × males SS) and (females SS × males RR) were available, two dominance levels were calculated.
[b] Resistance was also due to decreased cuticular penetration.

reduction of ALS activity. In some heterozygote individuals, this remaining activit is not sufficient to produce enough amino acids and resistance appears as semi dominant.

Channels and receptors

Sodium channels

Insensitive sodium channel provides usually a semi-recessive resistance, varyin from co-dominance to near-complete recessivity (Tab. 1). This recessivity has simple physiological explanation. The permanent opening of only a few Na^+Vdp (<0.1%) is sufficient to cause death (Narahashi, 1992). Heterozygous insects whic possess 50% of sensitive channels are therefore phenotypically similar to susceptibl insects in the presence of insecticide. One may predict that, in the case of a insecticide which will inhibit a ion channel by closing it (instead of opening it resistance will be co-dominant or dominant. This can be verified by considerin another insecticide target: the GABA-gated chloride channels.

Chloride channels

This class of receptors are differently affected by various insecticides: avermectin leave these channels permanently open whereas cyclodienes leave them in a close position (see Clark et al., 1995 for review). As expected, target-site resistance due t single pair base mutation (see ffrench-Constant et al., 1996 for review) to cyclod enes is usually found semi-dominant whereas resistance to avermectins is semi-re cessive (Tab. 1) as previously found for sodium channels.

δ-endotoxin receptors

Resistance to *Bacillus thuringiensis* mediated by binding site modifications in th moths *Plodia interpunctella* and *Plutella xylostella* and the tobacco butwori *Heliothis virescens* is inherited mostly as a semi-recessive trait (see Tab. 1). A δ-endotoxins create channels that disrupt ion regulation, we can tentatively explai the semi-recessivity by the same explanation given for sodium channels. If th formation of only a few pores is sufficient to cause death then, in heterozygotes, th 50% sensitive receptors would give sufficient pores to create osmotic swelling an cell lysis. More molecular data are required to settle this point.

Discussion

Our survey shows that pesticide resistance provided by target-site mutatior varies from recessivity to dominance and that specific and different molecul explanations could be found for each target-types.

Dominance of enzyme-target mutants

A general explanation for dominance conferred by modifications of enzymatic targe

Most cases of resistance conferred by AChE modifications are semi-dominan (Tab. 1). For ALS and KO reductase, only half of the mutations are semi-domi nant, but some of the dominant mutations would be classified as semi-dominant b comparing LC_{50} of each genotype rather than mortality ratio at a given insecticid concentration (see materials and methods). This general pattern can tentatively b explained by looking at the remaining enzyme activity as a function of pesticid concentration (Fig. 1A). In the absence of pesticide, all genotypes possess 100% o enzyme activity (Fig. 1A, part a). When pesticide concentration increases, sensitiv enzymes are progressively inhibited until enzyme activity is only provided b insensitive targets (Fig. 1A, part b). For these concentrations, the remaining activit is respectively 0, 50 and 100% for SS, RS and RR genotypes. We can define

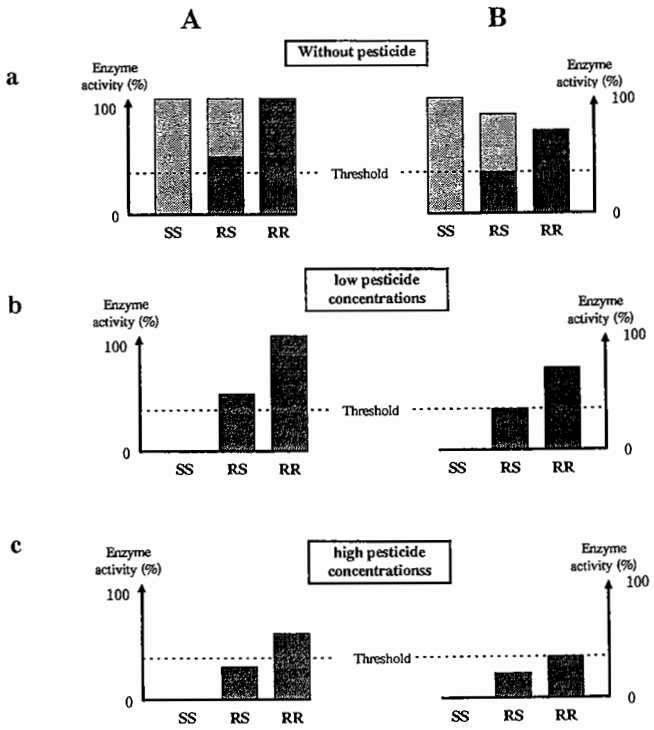

Fig. 1. Enzymatic activity in the absence (part a) or the presence (parts b and c) of two pesticic concentrations. The threshold indicates the minimum enzymatic compatible with life. ▩ and ▩ an represent enzymatic activities given by sensitive and insensitive targets respectively. Two situations a given: when enzymatic activity of insensitive enzyme-target is (B) or is not (A) altered.

threshold activity below which death occurs. Kacser and Burns (1981) have show that this threshold is usually below 50%. For example, AChE and ALS mutant with respectively 25% (Hoffman et al., 1992) and 10% (Falco and Dumas, 198 have been selected for, indicating a threshold well below 50%. Therefore, R individuals may survive the total inhibition of sensitive targets as their remainin 50% activity are sufficient to keep them alive. This explains why resistanc conferred by enzyme-target modifications is never found to be recessive (Tab. 1). I some cases, higher pesticide concentrations may inhibit (at least partly) insensitiv targets (Fig. 1A, part c). The remaining activity of RS individuals may eventuall fall below the threshold, homozygotes RR still have enough activity to be above (Fig. 1A, c). In this case, the R gene is recessive.

Usually a resistant enzymatic target displays a decrease in enzymatic activity compared to the wild type. This has been shown for AChE mutants in almost a insect pest species (review by Fournier and Mutero, 1994). Insensitive ALS are als often found with a decrease of enzymatic activity (e.g., Falco and Dumas, 198 Yadav et al., 1986). Therefore, in the absence of insecticide, RS and RR genotype possess a lower activity compared with SS (Fig. 1B, part a). As a consequence, i heterozygotes, once sensitive enzymes are completely inhibited, the remainin insensitive activity is lower than 50% (Fig. 1B, part b). In the mosquito *Cule pipiens*, insensitive AChE activity of some RS individuals account for less than 10 of the total AChE activity (Bourguet et al., 1997a). For such heterozygotes th inhibition of the sensitive counterpart drop the AChE activity below the threshol and resistance appears as semi-recessive (see Tab. 1). In all cases, the altere enzymatic activity of target mutants makes heterozygotes closer to the threshol once sensitive enzymes are fully inhibited, decreasing their resistance and hence th dominance level.

Dominance of insecticide resistance and W-K-B's theory

Actual dominance levels of pesticide resistance is given by comparing LC_{50} of th three genotypes. However, dominance levels predicted by W-K-B's theory is give by comparing mortality levels of the three genotypes at pesticide concentration that inhibit sensitive targets but without affecting insensitive enzymes (correspond ing to Fig. 1A, part b). For such concentrations, that kill SS individuals, th dominance level is given as $D = (M_{RS} - M_{SS})/(M_{RR} - M_{SS})$, where M_{SS}, M_{RS} an M_{RR} are the mortality ratio of SS, RS and RR genotypes, respectively. W-K-B theory predicts, $0.5 \leqslant D \leqslant 1$ depending of the Z value for the enzyme considere (see material and methods).

We tested W-K-B's prediction by comparing mortality ratio of RS and RR at pesticide concentration killing around 95% of SS individuals (*i.e.*, LC_{95}) and thu inhibiting almost all sensitive enzymes (*i.e.*, $e \approx 0$). We selected only R allele with resistance ratio >100 so that insensitive target is not affected by this pesticid concentration (as in Fig. 1, A or B, case b). We also removed all mutants associate with strong altered enzymatic activity. Twelve AChE mutants, four insensitive AL and one insensitive KO reductase were analyzed. All this modified enzymati targets were fully dominant ($D = 1$), which is in agreement with predictions c W-K-B's theory.

Dominance of channels and receptors

As recognized by Kacser and Burns (1981, p. 664), dominance of genes coding proteins other than enzymes or quasi-catalytic products is not predictable by W-K-B's theory: when an insecticide opens channels or creates pores, resistance is found to be mostly semi-recessive (Tab. 1), in agreement with the physiological function of the target. Identically, cyclodiene resistance conferred by GABA receptor is recessive when the insecticide leaves the channel open, and dominant when it leaves it closed, in agreement with our understanding of its physiological functioning. This is a general trend, and there are variations (Tab. 1) due probably to the occurrence of additional undetectable resistance mechanisms. This is particularly true for cyclodiene resistance, which is conferred by replacement of the same amino acid in most pest species (ffrench-Constant, 1994; ffrench-Constant et al. 1996), so that differences in dominance level across species are probably not explained by difference of target biochemical properties but rather by other additional molecular changes.

Evolution of dominance

The evolution of dominance was in part rejected since selection for the increase in frequency of a single modifier was thought to be ineffective. This was the conclusion of a dozen of theoretical analyses based on the mathematical model introduced by Wright (1929). However, Wagner and Bürger (1985) and Mayo and Bürger (1996) have shown that many of these analyses were incorrect, neglecting linkage disequilibrium and thus incapable of accurately predicting the course of change of the modifier frequency. Furthermore, Bürger (1983), using a complete non-linear analysis of Wright's mathematical model showed that the modifier always goes to fixation.

Curtsinger et al. (1994) and Mayo and Bürger (1997) have recently reviewed some cases of selection through visual predation on moths and butterflies that show evidence for the occurrence of modifier of dominance (e.g., Ford and Sheppard 1969; Mikkola, 1984). Both came to the conclusion that dominance relationships can be modified. Finally, the examples given here such as channels, enzymes in various complex pathways, etc. provide many opportunities for possible modifiers to interfere. The *smg* suppresser/enhancer genes of *Caenorhabditis elegans* is such an example. Mutations at these loci modify the dominance level of mutations at other loci (Hodgkin et al., 1989), indicating that the wild type *smg* loci encode proteins that can recognize and selectively degrade many mutant mRNAs. Although the extent of this surveillance system is not yet clear, Wilkie (1994) suggested that this degradation of mutant mRNA may in part explain the rarity of dominant lethal mutations.

In pesticide resistance, one may predict two major types of dominance modifiers. First, any mechanism increasing the activity of pesticide enzymatic targets. This would occur either through the selection of new, more active, resistant alleles, or

through the modification of gene expression altered by *cis*- or *trans*-acting control by duplication or amplification, or by post-translational modifications (reviewed by Taylor and Feyereisen, 1996). A second type of modifier would correspond to the selection of additional resistance mechanisms differentially affecting homozygotes (SS and RR) and heterozygotes (RS). Such modifiers have been described by Grigolo and Oppenoorth (1996) and Rupes and Pinterova (1975), who showed that in houseflies, a detoxification mechanism increased the degree of dominance of an insensitive target. They have found that the *recessive* resistance to DDT conferred by sodium channels modification (*kdr*) became more dominant in the presence of DDT-ase, a detoxifying enzyme which gives by itself only a low resistance level.

Conclusion

We have shown that dominance levels of pesticide resistance conferred by enzyme-target modifications may be roughly predicted. However, the actual dominance levels strongly depends on catalytic properties of each mutants, the threshold activity compatible with life and/or other interacting molecular mechanisms. Therefore, dominance of pesticide resistance conferred enzyme insensitivity always has molecular explanation but can not be simply predicted by W-K-B's theory. Hocking (1993) and Wilkie (1994) have also found several classes of molecular explanations for dominant mutations. Furthermore, when genes do not encode enzymes (like channels or receptors), physiological processes other than a simple enzymatic reaction or a linear enzymatic pathway have to be considered in order to understand how dominance is determined. Finally dominance can also be modified by environmental parameters (Bourguet et al., 1996a) or genetic mechanisms (see above). This raises the question: can a general theory of dominance ever be formulated? Although W-K-B's theory remains powerful in predicting the recessivity of deleterious mutations involved in some enzymatic pathways, no general theory emerges from the study of other situations and molecular explanations are to be sought on a case by case basis. As already suggested by Hodgkin (1993) "*There is no substitute for analysis at the molecular level*". Prediction of dominance level seems difficult without a minimal knowledge of how the gene product functions and without a minimal understanding of the link between genotypes and fitness components.

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