Review

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Climate change and the genetics of insecticide resistance

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Abstract

Changes in global temperature and humidity as a result of climate change are producing rapid evolutionary changes in many animal species, including agricultural pests and disease vectors, leading to changes in allele frequencies of genes involved in thermotolerance and desiccation resistance. As some of these genes have pleiotropic effects on insecticide resistance, climate change is likely to affect insecticide resistance in the field. In this review, we discuss how the interactions between adaptation to climate change and resistance to insecticides can affect insecticide resistance in the field using examples in phytophagous and hematophagous pest insects, focusing on the effects of increased temperature and increased aridity. We then use detailed genetic and mechanistic studies in the model insect, *Drosophila melanogaster*, to explain the mechanisms underlying this phenomenon. We suggest that tradeoffs or facilitation between adaptation to climate change and resistance to insecticides can alter insecticide resistance allele frequencies in the field. The dynamics of these interactions will need to be considered when managing agricultural pests and disease vectors in a changing climate.

Keywords: climate change; insecticide resistance; thermotolerance; desiccation; resistance; tradeoffs; facilitations

1 INTRODUCTION

Climate change is one of the most pressing issues of our time. Changes in the global climate such as increasing temperatures, elevated CO_2 levels, changes in UV radiation levels, and unpredictable changes to precipitation due to extreme weather events are dramatically impacting many habitats and ecosystems,[1] such as increasing aridity and the expansion of drylands in many regions.[2] Adaptation to these changing environmental conditions is producing rapid evolutionary changes in many animal species, including insects.[3] As a consequence of these evolutionary changes, agricultural insect pests and disease vectors undergo shifts in their geographic distributions and changes in their metabolic rates which may result in more generations per year.[3] It is predicted that the changing climate will lead to a decrease in crop yield due to the increase in damage caused by insect pests,[4] and an increase in the occurrences of vector-borne diseases,[5] prompting new challenges in the management of these pests.

The conventional use of synthetic insecticides to control agricultural insect pests and disease vectors began several decades ago and has been largely successful. However, as climate variables change, current strategies in using these chemicals may become less effective in controlling these pests. One hypothesis is that alterations in environmental conditions as a result of climate change may lead reduced insecticide efficacy as studies have shown that temperature can affect the toxicity of many insecticides used in pest management, leading to reduction in efficacy.[6] Another hypothesis is that evolutionary responses to climate change may result in rapid changes in the allele frequencies of genes involved in insecticide resistance. This is due to these insecticide resistance genes having pleiotropic effects on other traits, such as thermotolerance or desiccation resistance. Insecticide resistance and climate adaptation would therefore co-evolve. Changes in one trait can negatively or positively affect the other through tradeoffs or facilitation (Fig. 1).[7,8] In this review, we will discuss several studies detailing how climate change has affected insecticide resistance in phytophagous and hematophagous pest insects, focusing on the effects of increased temperature and increased aridity. The other effects of climate change, such as changes in CO_2 and UV radiation levels, are not discussed in this review but could also potentially affect the evolution of insecticide resistance. We then draw on detailed studies in the model insect, *Drosophila melanogaster*, to explain the genetic and molecular mechanisms underlying this phenomenon.

2 CLIMATE CHANGE AND INSECTICIDE RESISTANCE

Insects and other organisms often have numerous traits involved in climatic adaptation, including morphological variations and physiological variations such as changes in thermotolerance and desiccation resistance.[3] The interactions between these traits and insecticide resistance may influence selection responses in adapting to the dual challenges of climate change and insecticide use.[3] Evidence that climate can influence the evolution of resistance in the field is supported by modeling the association

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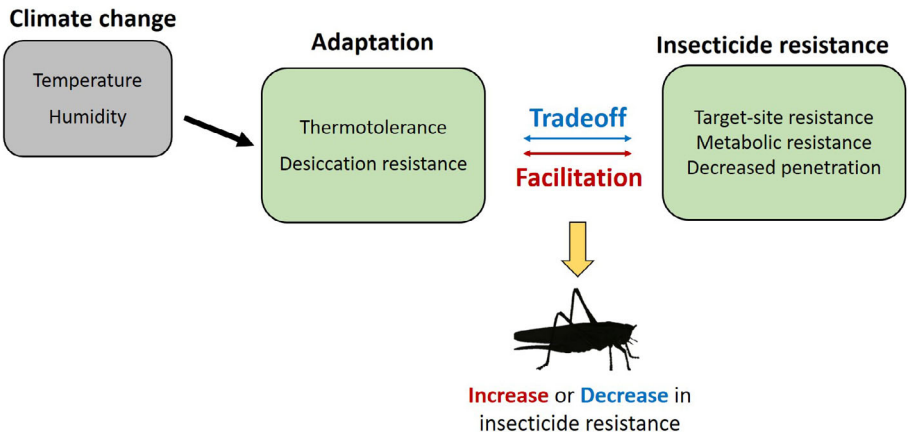

Figure 1. Adaptation to changes in temperature and humidity as a result of climate change may lead to tradeoffs or facilitation with insecticide resistance due to pleiotropy, shared genetic mechanisms or genetic linkage.

between long-term climatic data and insecticide usage or resistance data in specific regions. An analysis of pyrethroid resistance in the redlegged earth mite, *Halotydeus destructor*, a major pest of Australia's grain and pastoral industries, across many regions in Western Australia indicated that regional variations in aridity, temperature seasonality, and precipitation patterns affected the spatial pattern of resistance.[9] Another study modeling the development of deltamethrin resistance in *Triatoma infestans*, a Chagas disease vector, suggests that climate may influence the development of resistance in a region in Argentina.[10]

The effects of climate change in the development of insecticide resistance can be divided to two categories. The first category is that climatic adaptation imposes a fitness cost on insecticide resistance, resulting in fitness tradeoffs and the decrease of insecticide resistance alleles in the field. Laboratory studies that investigate the effects of these changing variables, such as elevated temperatures on insecticide resistance alleles, can be useful in informing how insecticide resistance may evolve as climate change occurs. For example, a laboratory study showed that higher temperatures impose a fitness cost on the chlorpyrifos-resistant strain of the diamondback moth, *Plutella xylostella*. Under heat stress, the resistant strain of *Plutella xylostella* has higher rates of wing vein damage and lower survival than the susceptible strain, suggesting a tradeoff between thermotolerance and insecticide resistance.[11] Similarly, in the brown planthopper, *Nilaparvata lugens*, a chlorpyrifos-resistant strain is associated with lower fitness compared to its susceptible counterparts at higher temperatures,[12] suggesting that a common genetic mechanism could underlie chlorpyrifos resistance and tradeoffs with thermotolerance in distant species. The second category is that climatic adaptation will also facilitate the development of insecticide resistance, resulting in an increase in insecticide resistance alleles. This facilitation is due to a common molecular basis underlying both climatic adaptation and insecticide resistance. Selection on one trait will therefore favor the other trait as well. One possible case is in the small brown planthopper, *Laodelphax striatellus*, where a positive association between buprofezin resistance and thermotolerance has been reported.[13] Another example is in the major malaria vector *Anopheles arabiensis*, where at elevated temperatures resistant individuals live longer than their susceptible counterparts, suggesting that insecticide resistance has increased fitness at higher temperatures.[14]

To determine why in some cases climate change may lead to a tradeoff with insecticide resistance and in other cases climate change may facilitate resistance, it is necessary to look at the genetic and molecular mechanisms underlying these different cases of insecticide resistance and the climatic factors involved.[7]

3 MECHANISMS UNDERLYING HOW CLIMATE CHANGE CAN AFFECT INSECTICIDE RESISTANCE

Different insecticide resistance mechanisms, including target site alterations, metabolic detoxification, decreased penetration, increased excretion, and behavioral alteration, allow insects to counter the toxic effects of insecticides.[15] Research on the genetic and molecular bases of these mechanisms in the past few decades has generally focused on two of these different modes of resistance: target-site resistance and metabolic resistance.[16] Target-site resistance is the result of genetic mutations in the target of the insecticide, rendering the insecticide unable to bind to the target or binding with less efficiency. These target genes encode ion channels such as γ-aminobutyric acid (GABA) receptors and voltage-gated sodium channels which are, for example, the target of pyrethroid insecticides.[17] Metabolic resistance usually occurs when there is increased activity of metabolic enzymes such as esterases, glutathione-*S*-transferases and cytochrome P450s[16]. This is usually due to evolution of *cis*-regulatory elements, which results in the overexpression of these metabolic genes,[9,18] or gene amplification, which increases the copy number of these genes.[20] In some cases, coding changes in these genes can also increase their enzymatic activity, resulting in higher rates of insecticide metabolism.[21] Alleles that confer target-site and metabolic resistance usually have elevated frequencies in populations under the selective pressure of continuous insecticide usage.[16,22]

3.1 Thermotolerance and insecticide resistance

As many genetic changes that confer insecticide resistance usually affect genes that normally have a primary function in insects, it is hypothesized that some resistance mutations may carry a fitness cost[7,8] due to the pleiotropic nature of these genes. One example is the gene encoding a GABA-gated chloride channel subunit, *Rdl* (Resistance to dieldrin). Substitutions of the alanine

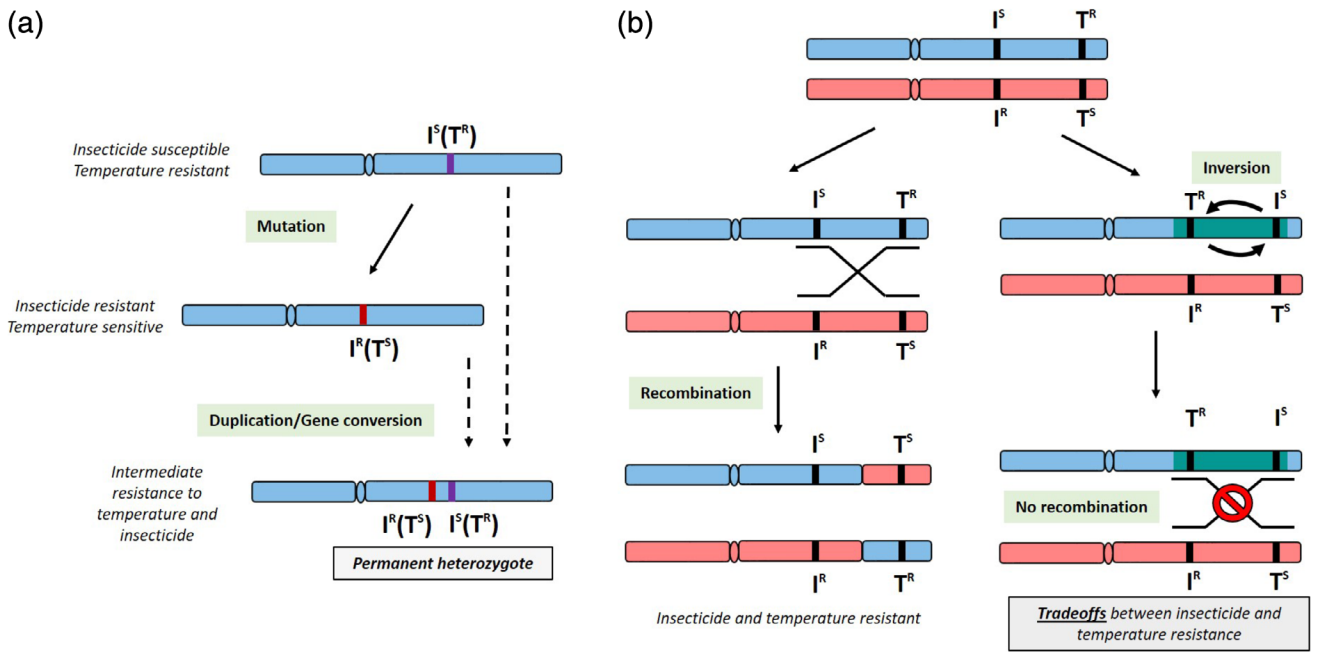

Figure 2. (a) Mutations in a single gene conferring insecticide resistance may lead to a temperature-sensitive phenotype as the gene has pleiotropic roles in both thermotolerance and insecticide resistance, leading to a tradeoff between these two traits. Some insects have evolved a state of 'permanent heterozygosity' at this locus by carrying both the insecticide susceptible allele (which does not have the temperature sensitive phenotype) and the resistant allele on a single chromosome, leading to intermediate insecticide resistance and intermediate thermotolerance. Examples of this include the *Rdl* gene in *Drosophila* and the *Ace-1* gene in mosquitoes. The *Ace-1* duplication is now found in all field-collected *Anopheles gambiae*. (b) In some cases, the tradeoffs between thermotolerance and insecticide resistance may occur on different genes. The dual selection of increased temperatures and insecticide usage would normally select for both insecticide-resistant and temperature-resistant alleles of these two genes, if chromosomal recombination is possible. However, the presence of chromosomal inversions in some natural insect populations leads to low or no recombination between these two genes, 'locking' the susceptible allele of one trait to the resistant allele of the other trait. This will lead to tradeoffs between the thermotolerance and insecticide resistance, restricting the spread of insecticide resistance as climate change occurs.

residue at position 302 in the *Rdl* gene confer high-level target-site resistance to cyclodiene insecticides in the vinegar fly, *Drosophila melanogaster*, but lead to a temperature-sensitive phenotype,[23] suggesting a fitness tradeoff between thermotolerance and insecticide resistance. The *Rdl* gene has been duplicated in many populations of *D. melanogaster*, with one copy carrying the susceptible allele and the other copy with the resistance mutation, resulting in intermediate resistance to dieldrin while alleviating the temperature sensitivity. This results in a state of permanent heterozygosity at this locus and could be an evolutionary strategy that manages the tradeoffs between the insecticide selection and thermal selection (Fig. 2(a)).[24] In many insect species, substitution at the same alanine residue also confers similar resistance to cylcodienes[25] and in some of these species *Rdl* is also duplicated.[24] This suggests that parallel evolution leading to similar mechanisms managing tradeoffs between insecticide resistance and thermotolerance could be a common occurrence in insect species at the *Rdl* locus, but further experimental evidence is needed. Another example showing that evolving permanent heterozygosity at insecticide resistance loci can be an evolutionary strategy to manage fitness cost associated with insecticide resistance is the acetylcholinesterase (*ace-1*) gene. Mutations in *ace-1* confer resistance to organophosphate and carbamate insecticides which are used in the control of the malaria mosquito *Anopheles gambiae*, but carry a fitness cost compared to the susceptible allele.[26] Permanent heterozygosity has evolved in this locus in all field-collected populations of *An. gambiae* from several African countries, resulting in mosquitoes with an immediate insecticide resistance phenotype. This leads to a large decrease in fitness cost associated with resistance, allowing this 'permanent heterozygous' allele to spread (Fig. 2(a)).[26]

In the absence of any tradeoffs and with continuous selective pressure from insecticide use, resistant alleles are beneficial and are predicted to reach fixation, which can be detected by examining selective sweeps around resistance loci.[27] However, if there is a tradeoff between thermotolerance and insecticide resistance, increases in resistant allele frequencies may be restricted in habitats with higher temperature, with susceptible alleles still persisting in populations. One example is the *Cyp6g1* locus in *D. melanogaster*. Overexpression of *Cyp6g1*, caused by the insertion of an *Accord* retrotransposon, confers resistance to 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) and multiple insecticides,[19,27] providing a strong fitness advantage in the face of insecticide use. However, the presence of the susceptible allele in populations suggests that tradeoffs could restrict the fixation of *Cyp6g1* resistance alleles. This is supported by a study showing latitudinal variation of *Cyp6g1* allele frequency,[28] suggesting that either temperature or local adaptation may affect allele frequencies. This locus has undergone a series of adaptive steps involving gene duplication and subsequent insertions of additional transposable elements, leading to an allelic series of increasing levels of DDT resistance.[29] A study comparing the effects of temperature and DDT on these different alleles suggests complex interactions in determining the fitness of these different *Cyp6g1* alleles.[30]

The example of *Cyp6g1* focused on a single locus. In reality, the interactions between climatic factors such as temperature and insecticide resistance are more complex, with multiple loci of large and small effects involved. A recent study undertook a

comprehensive population and quantitative genomics study of multiple field populations of *D. melanogaster* to investigate the complex genetic architecture of the tradeoff between insecticide resistance and temperature. Using *D. melanogaster* collected from four climatic extremes from Australia and North America, the authors performed a genome-wide association study focusing on Single nucleotide polymorphisms (SNPs) and transposable elements with resistance to imidacloprid, a widely used insecticide.[31] Two major loci were identified: the Nicotinic-Acetylcholine Receptor Alpha 3 (*nAChRα3*) gene, which is predicted to be involved in target-site resistance to neonicotinoids such as imidacloprid, and the Paramyosin (*Prm*) gene, which is predicted to encode an invertebrate muscle protein. The fitness of allelic deletions of both genes was tested in the presence of imidacloprid at two different temperatures, 20 and 30 °C. The deletion of *nAChRα3* increased susceptibility to imidacloprid at both temperatures while the deletion of *Prm* only increased susceptibility at 20 °C, suggesting that resistance conferred by this gene may be temperature dependent.[31]

In the same study, the authors also showed that chromosomal inversions are present at higher frequencies in areas with higher temperatures. One of these inversions, *In(3R)Payne*, has been shown previously to be associated with climate change adaptation and is present in higher frequencies in the warmer parts of Australia.[32] The authors showed that these chromosomal inversions harbor alleles associated with insecticide susceptibility. Because of the recombination-limiting genomic structures of these inversions, insecticide resistance alleles are unable to reach fixation in warmer areas as the inversion prevents or slows down the introgression of these resistant alleles. The tradeoffs between alleles that confer thermotolerance and alleles that confer insecticide resistance may therefore restrict the frequency of insecticide resistance alleles in warmer areas. Taken together, these data suggest that temperature increase from climate change may restrict the spread of imidacloprid resistance in natural populations of *D. melanogaster* due to tradeoffs with thermotolerance.[31] One of the important messages of this study is that tradeoffs between insecticide resistance and thermotolerance might not occur in a single gene or locus but could result from tradeoffs between different alleles of linked genes. Genes which are involved in thermotolerance and genes which are involved in insecticide resistance are 'locked' in genomic areas of reduced recombination, resulting from chromosomal inversions (Fig. 2(b)).[31] This study focused on a single insecticide, imidacloprid, and the model organism *D. melanogaster*, which is a non-target insect for insecticides.[31] Further studies in pest insects and other species focusing on different insecticides will be needed to assess how changes in temperature due to climate change will affect insecticide resistance in pest insects in the field.

3.2 Humidity, desiccation resistance, and insecticide pentration

In addition to increased global temperatures, climate change is also predicted to lead to erratic rainfall and drought across the planet. This may lead to an increase in aridity in many parts of the world, but an increase in humidity in other parts of the world.[1,2] This could lead to insects evolving mechanisms that withstand desiccation stress in areas with increasing aridity. The major mechanism underlying the evolution of desiccation resistance in insects is reducing water loss through the cuticle.[33] The layer of waxy cuticular hydrocarbons (CHCs), the outermost hydrophobic layer on the insect body surface, has an important role in controlling water loss by reducing the rate of evaporation through the cuticle. CHCs are synthesized in specialized oenocyte cells via the fatty acyl-CoA synthesis pathway involving a series of fatty acyl-CoA modification enzymes such as desaturases, elongases, and reductases that metabolize acetyl-CoA to alcohols and aldehydes before the final decarbonylation to long-chained hydrocarbons by a CYP4G cytochrome P450 enzyme.[34,35] Removing all CHCs by RNA interference (RNAi) knockdown of this CYP4G ortholog in *D. melanogaster*, *Cyp4g1*, resulted in severe desiccation sensitivity in *D. melanogaster*.[35] Variations in the composition and levels of CHCs between insects have also been positively associated with differences in desiccation resistance. The Australian habitat generalist *Drosophila* species, *D. serrata*, contains higher levels of methyl branched CHCs than its sibling species, the rainforest restricted specialist *D. birchii*. This higher level of methyl-branched CHCs underlies the significant higher desiccation resistance in *D. serrata* as compared to *D. birchii*.[36] Similarly, CHC differences in two widely distributed ant species, *Myrmica rubra* and *Myrmica ruginodis*, are correlated with desiccation resistance.[37]

What do CHCs and desiccation resistance have to do with insecticide resistance? As mentioned earlier, in addition to target-site and metabolic resistance, reduced insecticide penetration has also been suggested to be a mode of insecticide resistance.[15] Although reduced insecticide penetration has been documented in some species as a cause of insecticide resistance, a genetic mechanism underlying this mode of resistance has not been generally elucidated[20] until recently, when a mechanistic link between insecticide resistance due to reduced penetration and an increase in CHC production was first documented in the malaria mosquito, *An. gambiae*.[38] The authors first observed that resistant *An. gambiae* mosquitoes have a slower uptake of the insecticide deltamethrin. Using transmission electron microscopy, although the authors did not find any differences in overall cuticular thickness, they found that resistant mosquitoes have significantly thicker epicuticle, where the CHCs are located. The authors then measured CHC abundance and found that the resistant strain had higher amounts of CHCs compared to the susceptible strain. As two CYP4G homologs, *Cyp4g16* and *Cyp4g17*, are overexpressed in the resistant strain, the authors hypothesized that one of these CYP4G enzymes would be responsible for the increase in CHCs. Using an *in vitro* decarbonylase assay, they showed that *Cyp4g16* but not *Cyp4g17* can produce hydrocarbons in an insect cell system. In summary, the authors suggested that overexpression of *Cyp4g16* in resistant mosquitoes led to the increased production of CHCs on the epicuticle and a reduction in penetration of the insecticide deltamethrin.[38]

In a probable case of parallel evolution, a CYP4G homolog, *Cyp4g19*, was also overexpressed in a pyrethroid-resistant strain of the German cockroach, *Blattella germanica*, which showed decreased cuticular permeability to insecticides.[39] The expression of *Cyp4g19* was knocked down using RNAi, resulting in loss of CHCs and enhanced cuticular permeability, as well as increased mortality when treated with the insecticide beta-cypermethrin. Together, these two studies showed that resistance to pyrethroid insecticides can be due to the overexpression of CYP4G genes in diverse insect species, leading to an increase in CHC levels and reduced penetration of these insecticides. The *B. germanica* study also showed that the overexpression of *Cyp4g19* can be induced by desiccation stress, which may lead to lower penetration of beta-cypermethrin in *B. germanica*.[39] The functional link between susceptibility to desiccation and increased insecticide penetration was established in a recent study in the brown

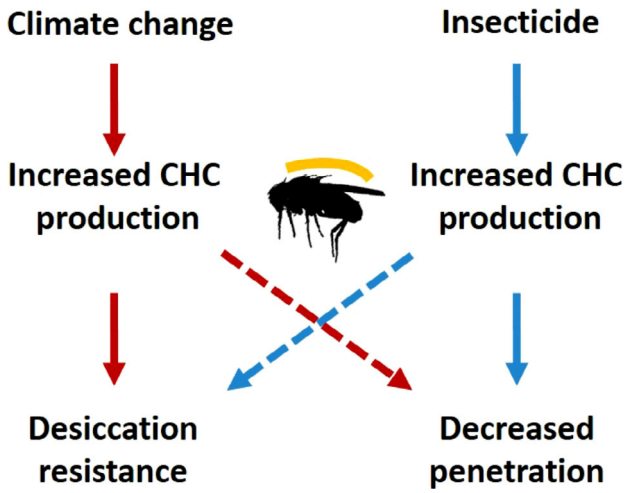

Figure 3. Either adaptation to a more arid environment or response to insecticide usage could lead to an increase in cuticular hydrocarbon (CHC) production, leading to a thicker epicuticle and both desiccation resistance and decreased insecticide penetration. In other words, adaptation to one stress would also facilitate adaptation to the other stress.

planthopper, *Nilaparvata lugens*. RNAi knockdown of two CYP4G homologs, *Cyp4g76* and *Cyp4g115*, in *N. lugens* led to the reduction of CHCs on the cuticle and to both a decrease in desiccation resistance and an increase in the penetration rates of four insecticides: pymetrozine, imidacloprid, thiamethoxam, and buprofezin. This study not only showed that the CHC layer can modulate both desiccation resistance and insecticide penetration, but also showed that this mechanism (cuticular penetration) may confer resistance to a range of different insecticide classes.[40]

As increases in CHC production are involved in both desiccation resistance and insecticide resistance due to reduced penetration, it is likely that selection for one trait would also select for the other (facilitation) (Fig. 3). As insects adapt to drier environments as a result of climate change, increase in CHC production and a thicker epicuticle may also lead to many insect species having increased insecticide resistance as a result of reduced insecticide penetration. Conversely, selection for insecticide resistance may lead to pre-adaptation for desiccation resistance and increased survival in arid environments, as well as changes in distribution for many insect species (Fig. 3). In addition to being involved in desiccation resistance and insecticide penetration, some CHCs are also contact pheromones involved in mate choice and mating success,[41] suggesting additional interactions or factors to consider in the evolution of reduced insecticide penetration. In both cases of CYP4G overexpression in *An. gambiae* and *B. germanica*, the frequency of the resistance allele in the field was not determined. Since the overexpression of the CYP4G gene can positively impact or facilitate both desiccation resistance and insecticide resistance, we would expect to see an increase in the frequency of the CYP4G overexpression alleles in many insect species over time as aridity increases as a result of climate change.

The above examples focus on the effects of CHCs on both desiccation resistance and insecticide penetration. Other genetic changes to the thickness or composition of the cuticle may affect insecticide penetration as well. A survey of insecticide resistance in different mosquito species as well as the agricultural pests *Heliothis virescens* and *Myzus persicae* showed that many genes related to cuticular functions are up-regulated in resistant strains of these species.[42] Although these mechanisms have not been functionally tested, it should be mentioned that these different mechanisms could also drive the evolution of insecticide resistance via decreased cuticular penetration and could co-evolve with adaptation to desiccation stress.

4 DISCUSSION

In this review, we discuss a handful of recent studies suggesting how climate change might affect the evolution of insecticide resistance in the field, focusing on the effects of climate change on global temperature and humidity. We suggest that, depending on the genetic mechanisms involved, climate change may lead to either an increase or a decrease in the frequency of resistant alleles in the field. This is due to these resistant alleles having pleiotropic effects on climatic adaptations such as thermotolerance and desiccation resistance.

How do we detect if climate change has affected insecticide resistance in the field? One method is to look at changes in allele frequency over time as climate change affects temperature and aridity. Climate change can produce shifts in allele frequency rapidly. Clinal studies of natural populations of *D. melanogaster* showed that thermotolerance varies latitudinally along a cline, and changes in the allele frequencies of genes associated with thermotolerance along this cline can be detected over relatively short amounts of time.[43] As some insecticide resistance alleles also show the same clinal variation,[28,29] if climate change has affected insecticide resistance allele frequency over time, then similar changes in allele frequency over time along a cline can be detected for insecticide resistance. It would also be interesting to revisit the previous sample sites of a large comprehensive study involving *D. melanogaster*[31] and repeat the experiments in a few decades to determine whether climate change has affected the allele frequency of these populations over time. Another method is to use long-term climatic data and insecticide usage records to build models that may predict how these two variables interact in the development of field resistance, as discussed in the introduction.[9,10]

It has long been hypothesized that insecticide resistance in the absence of continuous exposure has a fitness cost due to the pleiotropic effects of some of these genetic changes that confer insecticide resistance also affecting other traits, such as thermotolerance and desiccation resistance.[7] This could either increase or decrease insecticide resistance in the field as a result of tradeoffs or facilitation due to climate change. In some cases, insect species have escaped these tradeoffs through genome evolution leading to permanent heterozygosity in resistance loci such as the *Rdl* gene and the *Ace-1* gene, to balance the tradeoffs between thermotolerance and insecticide resistance.[24,26] This could be due to gene duplication followed by neo-functionalization, sub-functionalization, or the process of gene conversion. In other cases, these tradeoffs or facilitations may not be the consequences of changes in a single locus. The comprehensive study of *D. melanogaster* from four different locations showed that reduced recombination due to chromosomal inversions may lead to linked genes or alleles which are inherited together.[31] Such chromosomal blocks may contain alleles of genes that have opposite effects with regard to thermotolerance and insecticide resistance, leading to tradeoffs under the dual selection pressures of temperature and insecticide.

In the examples given in this paper, target-site and metabolic resistance against insecticides may have tradeoffs with thermotolerance, while increased penetration resistance facilitates or has a

positive effect on desiccation resistance. We do not know if this is the norm for all cases of target-site, metabolic or reduced penetration resistance, or if these are exceptions to the rule. However, due to the interactions between insecticide resistance and adaptation to climate change, we suggest that some modes of insecticide resistance may evolve more rapidly than others, as climate change alters environmental factors such as temperature and humidity. Although we separate the effects of thermotolerance and desiccation resistance in our review, we note that increasing temperature due to global warming may also place many insect species under desiccation stress due to increased water loss at elevated temperatures.[44]

Management of insecticide resistance in the future may need to consider the effects of climate change on resistant alleles. This includes understanding the genetic basis of each case of resistance and taking into account the regional changes in environmental factors resulting from climate change and modeling how insecticide resistance may evolve. Using insecticides or new formulations that have a different mechanism than the one which the insect species pre-adapted to as a result of climate change can also be a strategy.[45] Alternatively, non-insecticide management strategies such as biocontrol or cultural control should also be considered in managing insect pests in the face of climate change.[46]

Beyond insecticide resistance, some of the long-term impacts of climate change on our environments and ecosystems may be irreversible. We hope that our review contributes to increasing awareness of this very important issue that affects us and future generations.

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REFERENCES

1 Stott P, How climate change affects extreme weather events. *Science* **352**:1517–1518 (2016).
2 Schlaepfer DR, Bradford JB, Lauenroth WK, Munson SM, Tietjen B, Hall SA *et al.*, Climate change reduces extent of temperate drylands and intensifies drought in deep soils. *Nat Commun* **8**:14196 (2017).
3 Hoffmann AA and Sgro CM, Climate change and evolutionary adaptation. *Nature* **470**:479–485 (2011).
4 Deutsch CA, Tewksbury JJ, Tigchelaar M, Battisti DS, Merrill SC, Huey RB *et al.*, Increase in crop losses to insect pests in a warming climate. *Science* **361**:916–919 (2018).
5 Tjaden NB, Caminade C, Beierkuhnlein C and Thomas SM, Mosquito-borne diseases: advances in modelling climate-change impacts. *Trends Parasitol* **34**:227–245 (2018).
6 Matzrafi M, Climate change exacerbates pest damage through reduced pesticide efficacy. *Pest Manag Sci* **75**:9–13 (2019).
7 ffrench-Constant R and Bass C, Does resistance really carry a fitness cost? *Curr Opin Insect Sci* **21**:39–46 (2017).
8 Kliot A and Ghanim M, Fitness costs associated with insecticide resistance. *Pest Manag Sci* **68**:1431–1437 (2012).
9 Maino JL, Umina PA and Hoffmann AA, Climate contributes to the evolution of pesticide resistance. *Glob Ecol Biogeogr* **27**:223–232 (2018).
10 Fronza G, Toloza A, Picollo M, Carbajo A, Rodríguez S and Mougabure-Cueto G, Modelling the association between deltamethrin resistance in *Triatoma infestans* populations of the Argentinian Gran Chaco region with environmental factors. *Acta Trop* **194**:53–61 (2019).
11 Zhang LJ, Wu ZL, Wang KF, Liu Q, Zhuang HM and Wu G, Tradeoff between thermal tolerance and insecticide resistance in *Plutella xylostella*. *Ecol Evol* **5**:515–530 (2015).
12 Yang BJ, Liu ML, Zhang YX and Liu ZW, Effects of temperature on fitness costs in chlorpyrifos-resistant brown planthopper, *Nilaparvata lugens* (Hemiptera: Delphacidae). *Insect Sci* **25**:409–417 (2018).
13 Li Y, Zhang Y, Liu X and Guo H, Does resistance to buprofezin improve heat and cold tolerance of *Laodelphax striatellus* (Hemiptera: Delphacidae)? *Environ Entomol* **46**:988–994 (2017).
14 Oliver SV and Brooke BD, The effect of elevated temperatures on the life history and insecticide resistance phenotype of the major malaria vector *Anopheles arabiensis* (Diptera: Culicidae). *Malar J* **16**:73 (2017).
15 Wilson T, Resistance of *Drosophila* to toxins. *Annu Rev Entomol* **46**:545–571 (2001).
16 ffrench-Constant R, Daborn P and Le Goff G, The genetics and genomics of insecticide resistance. *Trends Genet* **20**:163–170 (2004).
17 Dong K, Du Y, Rinkevich F, Nomura Y, Xu P, Wang L *et al.*, Molecular biology of insect sodium channels and pyrethroid resistance. *Insect Biochem Mol Biol* **50**:1–17 (2014).
18 Pu J, Sun H, Wang J, Wu M, Wang K, Denholm I *et al.*, Multiple *cis*-acting elements involved in up-regulation of a cytochrome P450 gene conferring resistance to deltamethrin in small brown planthopper, *Laodelphax striatellus* (Fallén). *Insect Biochem Mol Biol* **78**:20–28 (2016).
19 Chung H, Bogwitz MR, McCart C, Andrianopoulos A, Ffrench-Constant RH, Batterham P *et al.*, Cis-regulatory elements in the *Accord* retrotransposon result in tissue-specific expression of the *Drosophila melanogaster* insecticide resistance gene *Cyp6g1*. *Genetics* **175**:1071–1077 (2007).
20 Puinean AM, Foster SP, Oliphant L, Denholm I, Field LM, Millar NS *et al.*, Amplification of a cytochrome P450 gene is associated with resistance to neonicotinoid insecticides in the aphid *Myzus persicae*. *PLoS Genet* **6**:e1000999 (2010).
21 Ibrahim SS, Riveron JM, Bibby J, Irving H, Yunta C, Paine MJ *et al.*, Allelic variation of cytochrome P450s drives resistance to bednet insecticides in a major malaria vector. *PLoS Genet* **11**:e1005618 (2015).
22 Weedall GD, Mugenzi LM, Menze BD, Tchouakui M, Ibrahim SS, Amvongo-Adjia N *et al.*, A cytochrome P450 allele confers pyrethroid resistance on a major African malaria vector, reducing insecticide-treated bednet efficacy. *Sci Transl Med* **11**:eaat7386 (2019).
23 ffrench-Constant R, Steichen J and Ode P, Cyclodiene insecticide resistance in *Drosophila melanogaster* (Meigen) is associated with a temperature-sensitive phenotype. *Pestic Biochem Physiol* **46**:73–77 (1993).
24 Remnant EJ, Good RT, Schmidt JM, Lumb C, Robin C, Daborn PJ *et al.*, Gene duplication in the major insecticide target site, Rdl, in *Drosophila melanogaster*. *Proc Natl Acad Sci USA* **110**:14705–14710 (2013).
25 ffrench-Constant R, The molecular and population genetics of cyclodiene insecticide resistance. *Insect Biochem Mol Biol* **24**:335–345 (1994).
26 Assogba BS, Milesi P, Djogbénou LS, Berthomieu A, Makoundou P, Baba-Moussa LS *et al.*, The ace-1 locus is amplified in all resistant *Anopheles gambiae* mosquitoes: fitness consequences of homogeneous and heterogeneous duplications. *PLoS Biol* **14**:e2000618 (2016).
27 Battlay P, Leblanc PB, Green L, Garud NR, Schmidt JM, Fournier-Level A *et al.*, Structural variants and selective sweep foci contribute to insecticide resistance in the *Drosophila* genetic reference panel. *G3 (Bethesda)* **8**:3489–3497 (2018).
28 Turner TL, Levine MT, Eckert ML and Begun DJ, Genomic analysis of adaptive differentiation in *Drosophila melanogaster*. *Genetics* **179**:455–473 (2008).
29 Schmidt JM, Good RT, Appleton B, Sherrard J, Raymant GC, Bogwitz MR *et al.*, Copy number variation and transposable elements feature in recent, ongoing adaptation at the *Cyp6g1* locus. *PLoS Genet* **6**:e1000998 (2010).
30 Fournier-Level A, Neumann-Mondlak A, Good R, Green L, Schmidt JM and Robin C, Behavioural response to combined insecticide and temperature stress in natural populations of *Drosophila melanogaster*. *J Evol Biol* **29**:1030–1044 (2016).

31 Fournier-Level A, Good RT, Wilcox SA, Rane RV, Schiffer M, Chen W *et al.*, The spread of resistance to imidacloprid is restricted by thermotolerance in natural populations of *Drosophila melanogaster*. *Nat Ecol Evol* **3**:647–656 (2019).

32 Rane RV, Rako L, Kapun M, Lee SF and Hoffmann AA, Genomic evidence for role of inversion 3 RP of *Drosophila melanogaster* in facilitating climate change adaptation. *Mol Ecol* **24**:2423–2432 (2015).

33 Gibbs AG and Matzkin LM, Evolution of water balance in the genus *Drosophila*. *J Exp Biol* **204**:2331–2338 (2001).

34 Finet C, Slavik K, Pu J, Carroll SB and Chung H, Birth-and-death evolution of the fatty acyl-CoA reductase (FAR) gene family and diversification of cuticular hydrocarbon synthesis in *Drosophila*. *Genome Biol Evol* **11**:1541–1551 (2019).

35 Qiu Y, Tittiger C, Wicker-Thomas C, Le Goff G, Young S, Wajnberg E *et al.*, An insect-specific P450 oxidative decarbonylase for cuticular hydrocarbon biosynthesis. *Proc Natl Acad Sci USA* **109**:14858–14863 (2012).

36 Chung H, Loehlin DW, Dufour HD, Vaccarro K, Millar JG and Carroll SB, A single gene affects both ecological divergence and mate choice in *Drosophila*. *Science* **343**:1148–1151 (2014).

37 Sprenger PP, Burkert LH, Abou B, Federle W and Menzel F, Coping with the climate: cuticular hydrocarbon acclimation of ants under constant and fluctuating conditions. *J Exp Biol* **221**:jeb171488 (2018).

38 Balabanidou V, Kampouraki A, MacLean M, Blomquist GJ, Tittiger C, Juárez MP *et al.*, Cytochrome P450 associated with insecticide resistance catalyzes cuticular hydrocarbon production in *Anopheles gambiae*. *Proc Natl Acad Sci USA* **113**:9268–9273 (2016).

39 Chen N, Pei XJ, Li S, Fan YL and Liu TX, Involvement of integument-rich CYP4G19 in hydrocarbon biosynthesis and cuticular penetration resistance in *Blattella germanica* (L.). *Pest Manag Sci:Early view* 76:215-226 (2019).

40 Wang S, Zhang D and Li B, NlCYP4G76 and NlCYP4G115 modulate susceptibility to desiccation and insecticide penetration through affecting Cuticular hydrocarbon biosynthesis in *Nilaparvata lugens* (Hemiptera: Delphacidae). *Front Physiol* **10:913** (2019).

41 Chung H and Carroll SB, Wax, sex and the origin of species: dual roles of insect cuticular hydrocarbons in adaptation and mating. *Bioessays* **37**:822–830 (2015).

42 Balabanidou V, Grigoraki L and Vontas J, Insect cuticle: a critical determinant of insecticide resistance. *Curr Opin Insect Sci* **27**:68–74 (2018).

43 Umina P, Weeks A, Kearney M, McKechnie S and Hoffmann A, A rapid shift in a classic clinal pattern in *Drosophila* reflecting climate change. *Science* **308**:691–693 (2005).

44 Gibbs AG and Rajpurohit S, Cuticular lipids and water balance, in *Insect hydrocarbons : biology, biochemistry, and chemical ecology*, ed. by Blomquist GJ and Bagnères A-G. Cambridge University Press, Cambridge, New York, pp. 100–120 (2010).

45 Sparks TC and Nauen R, IRAC: mode of action classification and insecticide resistance management. *Pestic Biochem Physiol* **121**:122–128 (2015).

46 Andrew NR and Hill SJ, Effect of climate change on insect pest management, in *Environmental Pest Management: Challenges for Agronomists, Ecologists, Economists and Policymakers*, ed. by Coll M and Wajnberg E. Wiley,Hoboken, NJ, pp. 197–223 (2017).

