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Impact of environment on mosquito response to pyrethroid insecticides: Facts, evidences and prospects

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ABSTRACT

By transmitting major human diseases such as malaria, dengue fever and filariasis, mosquito species represent a serious threat worldwide in terms of public health, and pose a significant economic burden for the African continent and developing tropical regions. Most vector control programmes aiming at controlling life-threatening mosquitoes rely on the use of chemical insecticides, mainly belonging to the pyrethroid class. However, resistance of mosquito populations to pyrethroids is increasing at a dramatic rate, threatening the efficacy of control programmes throughout insecticide-treated areas, where mosquito-borne diseases are still prevalent. In the absence of new insecticides and efficient alternative vector control methods, resistance management strategies are therefore critical, but these require a deep understanding of adaptive mechanisms underlying resistance. Although insecticide resistance mechanisms are intensively studied in mosquitoes, such adaptation is often considered as the unique result of the selection pressure caused by insecticides used for vector control. Indeed, additional environmental parameters, such as insecticides/pesticides usage in agriculture, the presence of anthropogenic or natural xenobiotics, and biotic interactions between vectors and other organisms, may affect both the overall mosquito responses to pyrethroids and the selection of resistance mechanisms. In this context, the present work aims at updating current knowledge on pyrethroid resistance mechanisms in mosquitoes and compiling available data, often from different research fields, on the impact of the environment on mosquito response to pyrethroids. Key environmental factors, such as the presence of urban or agricultural pollutants and biotic interactions between mosquitoes and their microbiome are discussed, and research perspectives to fill in knowledge gaps are suggested.

1. Introduction

Mosquito-borne diseases, such as malaria, filariasis and a plethora of viruses dramatically affect public health and represent a major burden in terms of economy and development worldwide (WHO, 2011). Anopheline mosquitoes, such as *Anopheles funestus* or the two complex sibling species, *Anopheles gambiae sensu stricto* and *Anopheles gambiae arabiensis*, are major vectors of *Plasmodium* parasites causing malaria. In 2010, an estimated 3.3 billion people were at risk of malaria, mostly in African countries with up to 210 million cases and 655,000 fatalities (WHO, 2011). Similarly, *Aedes* mosquitoes, such as *Aedes aegypti* and *Aedes albopictus*, vectors of Dengue, Chikungunya and yellow fever viruses, represent increasing health issues (Gubler, 2002; Gratz, 2004). Moreover, *Culex* mosquitoes also transmit several diseases including filariasis and encephalitis (Hayes et al., 2005).

Most vector control programmes largely rely on the application of chemical insecticides by the use of outdoor spraying, impregnated nets (ITNs) or indoor residual spraying (IRS). Different classes of insecticides have been successively used since 1950s, but most current control programmes are largely dependent on synthetic pyrethroids, which are the only WHO-recommended insecticides for ITNs (WHO, 2006). However, pyrethroid efficacy is now threatened by the rise of resistance in target populations. Such phenomenon is occurring worldwide in all major disease vector mosquito species and spreads at a rapid rate (Harris et al., 2010; Marcombe et al., 2009a,b; Ranson et al., 2009).

Pyrethroid resistance is believed to be mainly caused by high ITNs and IRS coverage, or recurrent space spraying interventions

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(Balkew et al., 2010; Marcombe et al., 2011; N'Guessan et al., 2007; Protopopoff et al., 2008). However, studies pointed out the possible role of other factors in the selection of inherited resistance mechanisms or in the higher tolerance of mosquitoes to pyrethroids. Among them, insecticide use for personal protection and for controlling crop pests in agriculture has often been suggested as additional selective pressures favouring pyrethroid resistance. Other studies associated a higher pyrethroid tolerance of mosquitoes and the presence of anthropogenic pollutants in urban, agricultural or industrial areas. Although poorly studied in mosquitoes yet, the impact of plant chemicals on insecticide resistance has been confirmed in herbivorous insects and might affect pyrethroid resistance mechanisms in mosquitoes. Indeed, mosquito larvae often feed on plant debris or grow in water bodies enriched with plant compounds and interactions between these xenobiotics and insecticide tolerance or mosquito detoxification pathways have been described (David et al., 2006; Shaalan et al., 2005). In addition to abiotic factors, biotic interactions taking place among mosquitoes, pathogens they transmit and their microbiome (microbes that inhabit the insect) may also occur. Such microorganisms range from symbionts to opportunistic entomopathogens, and have the potential to affect several physiological host processes such as detoxification systems (Behura et al., 2011; Félix et al., 2010) or confer insecticide resistance (Kikuchi et al., 2012).

Current environmental trends including climate change, increased exchanges and urbanization, affect the distribution of disease vectors and subsequently the transmission and incidence of human pathogens (Gould and Higgs, 2009; Peterson et al., 2005). In this context, the present work aims at updating current knowledge on pyrethroid resistance mechanisms in mosquitoes and reviewing existing data related to the impact of environmental factors such as urban and agricultural pollutants or biotic factors on mosquito response to pyrethroids, and try to explain how such factors could affect resistance. For each factor, molecular mechanisms leading to resistance or increased tolerance to pyrethroids are discussed.

2. Pyrethroid resistance mechanisms in mosquitoes

Resistance of insects to insecticides can be the consequence of various physiological changes, such as mutations of the proteins targeted by the insecticide (target-site insensitivity) (Hemingway and Ranson, 2000), a lower penetration or sequestration, or an increased biodegradation of the insecticide due to enhanced detoxification activities (metabolic resistance) (Hemingway et al., 2004). Resistance of mosquitoes to pyrethroids appears to rely mainly on target-site and metabolic resistance mechanisms, although the role of other mechanisms, such as cuticular resistance is likely (Fig. 1). All these mechanisms can occur simultaneously in resistant populations with cumulative phenotypic effects leading to resistance to a single or multiple insecticides.

2.1. Target-site mutations

Mutations in the target site proteins are probably the best understood pyrethroid resistance mechanism found in insects, and involve non-synonymous mutations of the gene encoding the paratype voltage-gated sodium channel (VGSC) expressed in the insect central nervous system targeted by pyrethroids (Soderlund, 2008). These mutations are often referred to 'knock down resistance' (kdr) mutations due to their association with a reduction of the knock-down effect (*i.e.* temporary paralysis of the insect occurring shortly after contact with pyrethroids). Kdr mutations can also be selected by and do confer cross-resistance to the notorious organochlorine DDT, which also targets the insect VGSC (Burton et al., 2011; Soderlund, 2008). In the major African malaria vector *An. gambiae*, two distinct mutations in the S6 transmembrane segment of domain II of the VGSC at position 1014 have been identified, leading to amino acid residue changes from a leucine to a phenylalanine in West Africa (L1014F), and a leucine to a serine in East Africa (L1014S) (Donnelly et al., 2009; Martinez-Torres et al., 1998; Ranson et al., 2000). Recently, another mutation in the linker between domains III–IV of the VGSC (N1575Y) linked to pyrethroid resistance phenotype in *An. gambiae* has been identified in west and central Africa (Jones et al., 2012). This mutation, strongly associated to the L1014F mutation, was found in both M and S molecular forms and authors suggested that this new mutation can compensate for L1014F deleterious effects or confer additional resistance to insecticides targeting the VGSC. To date, no kdr mutation has been detected in the other major malaria vector, *An. funestus*, where metabolic resistance mechanisms appear predominant (Amenya et al., 2008; Cuamba et al., 2010; Morgan et al., 2010; Okoye et al., 2008). Multiple kdr mutations have also been identified in other vectors, such as *Ae. aegypti* (I1011M/V, V1016G/I and F1269C) (Brengues et al., 2003; Kawada et al., 2009; Saavedra-Rodriguez et al., 2007), *Culex pipiens* (L1014F/S) (Martinez-Torres et al., 1999), or more recently *Ae. albopictus* (F1534C) (Kasai et al., 2011). One should note that, although the frequency of kdr mutations is always associated with insecticide selection pressure in mosquitoes, their relative importance regarding resistance to different pyrethroid molecules has often

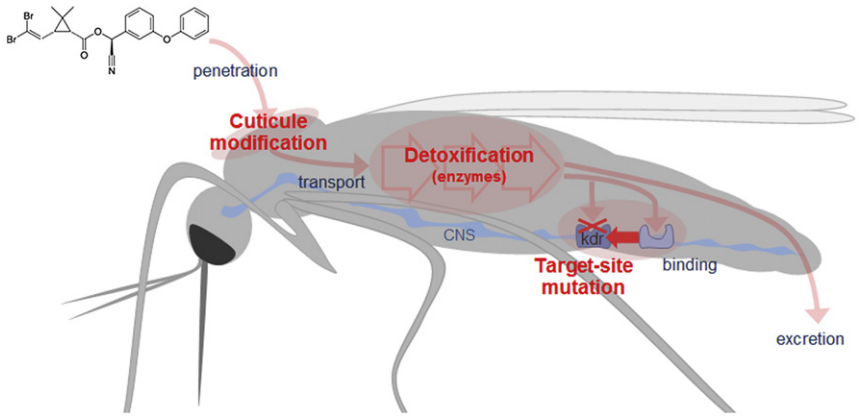

Fig. 1. Main toxicity steps of pyrethroid insecticides and associated resistance mechanisms in mosquitoes. CNS: central nervous system. The pyrethroid molecule represented is deltamethrin.

been questioned (Brooke and Koekemoer, 2010; Nwane et al., 2009; Ramphul et al., 2009; Reimer et al., 2008; Verhaeghen et al., 2010).

2.2. Enhanced insecticide detoxification

By contrast to target site resistance, metabolic resistance is a more dynamic process, involving potent regulation of the mosquito detoxification system in order to counteract the chemical aggression caused by insecticides. Metabolic resistance consists of elevated levels or enhanced activities of insecticide-detoxifying enzymes in resistant insects, resulting in a sufficient proportion of insecticide molecules being metabolized before reaching their target in mosquito nervous system (Brooke and Koekemoer, 2010). Such mechanism originally derived from the plant-insect evolutionary arm race (see Section 5) has been associated to resistance to various plant toxins and all types of chemicals, including insecticides (Despres et al., 2007; Feyereisen, 2012; Li et al., 2007; Scott, 1999). Detoxification enzymes typically linked to insecticide resistance include 3 major gene families, the cytochrome P450 monooxygenases (P450s or CYPs), the carboxyl/choline esterases (CCEs) and the glutathione *S*-transferases (GSTs), but other enzyme families may also be involved such as UDP glucosyl-transferases (UGTs) (Hemingway et al., 2004; Li et al., 2007). Insecticide detoxification can be the consequence of the over-production or structural modification of a single enzyme, but different enzymes from the same or different families can also act together simultaneously or sequentially to confer resistance. To date, most studies were focussed on the over-production of detoxification enzymes while the selection of particular detoxification enzyme alleles conferring enhanced insecticide degradation has rarely been studied in mosquitoes (Hardstone et al., 2010). Such knowledge gap can now be overcome by the use of high throughput sequencing approaches such as RNAseq, allowing to recover information on gene expression and nucleotide variations over the whole transcriptome from a single experiment (Bonizzoni et al., 2012; David et al., 2010; Vontas et al., 2010).

2.2.1. Cytochrome P450 monooxygenases

P450s are Phase I detoxification heme-thiolate enzymes catalysing various reactions, but are best known for their monooxygenase activity, introducing reactive or polar groups into xenobiotics or endogenous compounds (Feyereisen, 2012; Scott, 1999; Werck-Reichhart and Feyereisen, 2000). Mosquito genomes revealed a large expansion of the P450 gene family with more than 100 *CYP*s identified in *An. gambiae* (Ranson et al., 2002), 160 in *Ae. aegypti* (Strode et al., 2008) and more than 200 genes in *Culex quinquefasciatus* (Yang and Liu, 2011). Elevated levels of P450 activity have frequently been observed in pyrethroid-resistant mosquito populations (Hemingway et al., 2004). These enzymes are also known for their ability to be induced by a wide range of xenobiotics (Feyereisen, 2012). Following the development of the 'Anopheles Detox Chip' microarray (David et al., 2005), several mosquito *CYP*s over-transcribed in resistant field populations or laboratory colonies were identified by microarray analysis (Bariami et al., 2012; Christian et al., 2011; David et al., 2005; Djouaka et al., 2008; Itokawa et al., 2011; Komagata et al., 2010; Liu et al., 2007; Marcombe et al., 2009a,b, 2012; Mitchell et al., 2012; Muller et al., 2007, 2008; Poupardin et al., 2012; Saavedra-Rodriguez et al., 2012; Shen et al., 2003; Strode et al., 2008; Wondji et al., 2009; Wu et al., 2004; Yang and Liu, 2011). Several CYP genes were also linked to pyrethroid resistance by positional cloning and QTL approaches (Irving et al., 2012; Ranson et al., 2004; Saavedra-Rodriguez et al., 2008; Wondji et al., 2007). Among these candidates, some have been validated as pyrethroid metabolizers, including *An. gambiae* CYP6M2 and CYP6P3 (Muller et al., 2008; Stevenson et al., 2011), *Anopheles minimus* CYP6AA3 and CYP6P7 (Boonsuepsakul et al., 2008; Duangkaew et al., 2011) and *Ae. aegypti* CYP9J32, J24, J26 and J28 (Stevenson et al., 2011).

2.2.2. Carboxyl/choline esterases

CCEs can catalyse the hydrolysis of ester bonds, and are usually represented by more than 40 genes in mosquitoes (Ranson et al., 2002; Strode et al., 2008). Over-production of these enzymes has been frequently associated with insecticide resistance in various insects (Hemingway et al., 2004). Although CCEs have been mostly associated to organophosphate resistance in mosquitoes, their role in pyrethroid resistance is probable. Indeed, the ability of esterases to metabolize pyrethroids is well known in mammals (Godin et al., 2006; Nakamura et al., 2007; Ross et al., 2006; Takaku et al., 2011; Yang et al., 2009) and has also been proposed in mosquitoes (Vontas et al., 2005). Recently, the capacity of *Ae. aegypti* CCEs to metabolize pyrethroids has been demonstrated *in vitro* (Somwang et al., 2011). However, no specific mosquito CCE has yet been validated as a pyrethroid metabolizer.

2.2.3. Glutathione S-transferases

GSTs are Phase II detoxification enzymes capable of conjugating reduced glutathione to various chemical substrates. Around thirty GST genes from different subfamilies have been identified in mosquitoes (Ranson et al., 2002; Strode et al., 2008). Elevated levels of GSTs have been frequently involved in insecticide resistance, as being over-transcribed in pyrethroid resistant populations (David et al., 2005; Enayati et al., 2005; Marcombe et al., 2012; Muller et al., 2007, 2008; Ranson and Hemingway, 2005; Strode et al., 2008). In mosquitoes, members of epsilon GST subfamily have been shown to catalyse the dehydrochlorination of DDT (Lumjuan et al., 2005, 2011; Ortelli et al., 2003). A recent study showed that the partial RNA interference-mediated knock down of *Ae. aegypti GSTe7* and *GSTe2* genes led to an increased susceptibility to the pyrethroid deltamethrin (Lumjuan et al., 2011). Other studies suggested their potential role against oxidative stress (Vontas et al., 2001) and in pyrethroid sequestration (Kostaropoulos et al., 2001). Although the role of mosquito GSTs in pyrethroid resistance is likely, understanding underlying mechanisms requires further investigations.

2.3. Cuticular resistance

Cuticular resistance is characterized by a modification of the insect cuticle leading to a slower penetration of the insecticide reducing the amount of insecticide molecules within the insect. Such resistance mechanism has been evidenced in the cotton bollworm *Helicoverpa armigera* regarding pyrethroids (Ahmad et al., 2006; Gunning et al., 1995). Cuticle thickening linked to pyrethroid resistance has also been identified in the oriental fruit fly *Bactrocera dorsalis* (Lin et al., 2012). In mosquitoes, cuticular resistance is often mentioned, but has rarely been characterized. A recent study demonstrated a better tolerance of *An. funestus* to pyrethroids in association with an increased thickness of the cuticle (Wood et al., 2010). Such mechanism was later supported by a transcriptome-wide analysis identifying one cuticle gene over-transcribed in the resistant strain (Gregory et al., 2011). Genes encoding cuticle proteins (*CPLC8* and *CPLC#*) were also found over-transcribed in *An. gambiae* populations resistant to pyrethroids from Nigeria (Awolola et al., 2009). Using RNAseq, Bonizzoni et al. (2012) identified a gene encoding a cuticular protein with a chitin-binding motif (AGAP006009, CRP30) over-transcribed in pyrethroid resistant adult mosquitoes (Bonizzoni et al., 2012). In *Ae. aegypti*, selecting mosquito larvae in the laboratory for several generations with the neonicotinoid insecticide imidacloprid led to the constitutive over-transcription of multiple genes encoding cuticle proteins (Riaz et al., in press).

2.4. Environmental factors potentially affecting mosquito response to pyrethroids

The selection of kdr mutations is highly dependent on the use of insecticides targeting the sodium channel (*i.e.* DDT and pyrethroids), and thus could be affected by agricultural practices and domestic usage based on these insecticides. By contrast, enhanced detoxification is more complex, being probably affected by pesticides usage in agriculture, but also by the presence of various anthropogenic or natural xenobiotics present in mosquito breeding sites. Indeed, interactions between xenobiotics such as heavy metals (copper), polycyclic aromatic hydrocarbons (fluorenathene, benzo[a]pyrene) or herbicides (glyphosate and atrazine), and the expression of mosquito genes encoding detoxification enzymes have been demonstrated (Poupardin et al., 2008, 2012; Riaz et al., 2009). Regarding cuticular resistance, considering that most insecticides are lipophilic molecules, it is likely that such mechanism can be selected by and confers cross-resistance to multiple insecticides, including those used in agriculture. Altered expression of genes encoding cuticular proteins due to the presence of pollutants or pesticide residues has been described in mosquito larvae (David et al., 2010; Riaz et al., in press). From a broader view, it can be hypothesized that any xenobiotic affecting mosquito cuticle formation, composition or dynamics may interfere with this resistance mechanism. Finally, it was recently demonstrated that insect microflora can contribute to insecticide resistance (Kikuchi et al., 2012) and biotic interactions affecting mosquito response to pyrethroids cannot be excluded. Potential interactions between these factors and mosquito response to pyrethroids are discussed below and presented in Fig. 2.

3. Impact of agriculture

Agriculture is one of the most important economic sectors in Africa, accounting for 60% of employment with large areas of intensive agriculture, and about three-fifth of the farmers practicing small scale farming with routine usage of pesticides. Several studies suggested that the use of insecticides in agriculture contributed to the selection of resistance in mosquitoes, threatening the efficacy of vector control programmes (Chouaibou et al., 2008; Diabate et al., 2002; Yadouleton et al., 2009, 2011). Indeed, most insecticides used in agriculture are of the same chemical classes and have the same targets and modes of action as those used for vector control (Khambay and Jewess, 2010). Furthermore, pyrethroids are now widely used to protect crops against pest insects (Khambay and Jewess, 2010), and have the potential to select for resistance to pyrethroids used for controlling mosquitoes.

For instance, the Moshi Tanzania district has a historical recording of intensive agriculture (*e.g.* rice, coffee, sugar cane) with massive use of insecticides of various classes, but a moderate insecticide pressure from vector control activities. It was recently proposed that the high metabolic resistance of *Anopheles gambiae arabiensis* to pyrethroids in this area has been favoured by agriculture practices (Matowo et al., 2010). In West Africa, the increased rate of pyrethroid resistance and kdr mutation frequency were often attributed to the massive use of DDT and pyrethroids in cotton growing farms (Chandre et al., 1999; Chouaibou et al., 2008; Diabate et al., 2002; Ranson et al., 2009; Yadouleton et al., 2011). In Benin, it was reported that *An. gambiae* females frequently lay eggs in breeding sites located around agricultural settings (Akogbeto et al., 2006). The authors further suggested that larvae from these sites underwent selection pressure from agricultural pesticides, favouring the emergence of resistance.

In addition to intensive agriculture, the rapid growth of African cities also led to the development of small-scale urban agriculture with uncontrolled use of insecticides, potentially contributing to the resistance of mosquitoes to pyrethroids (Keiser et al., 2004; Yadouleton et al., 2009). In Cameroon, a recent study conducted in two major cities, Yaoundé and Douala, revealed that *An. gambiae* populations collected in cultivated areas were more resistant to the pyrethroid permethrin and DDT, compared to those from other breeding sites. This higher resistance was associated with a higher frequency of the kdr mutation, although the presence of metabolic mechanisms was not investigated (Antonio-Nkondjio et al., 2011). In Martinique island (French West Indies), *Ae. aegypti* populations show high resistance level to pyrethroids due to both target-site

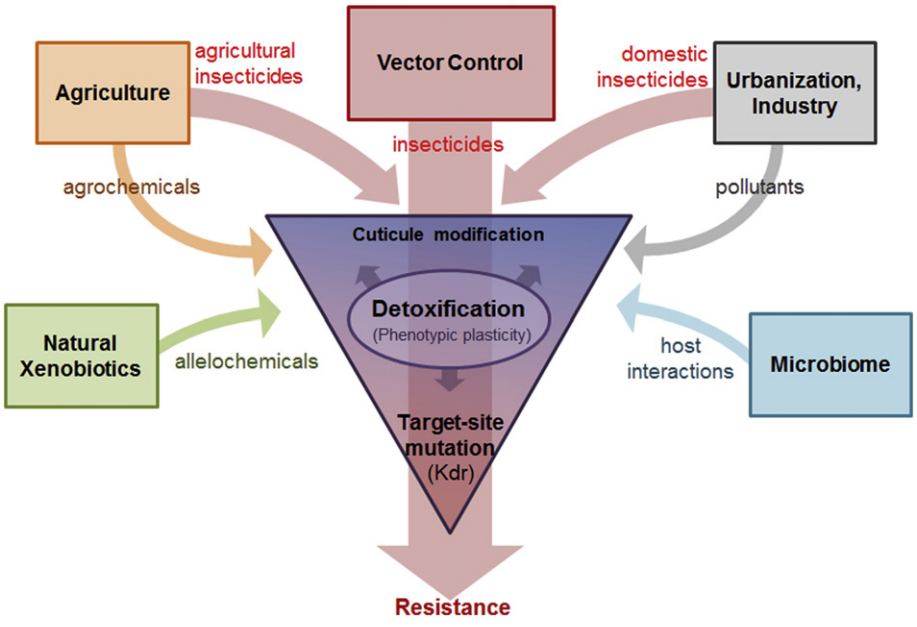

Fig. 2. Schematic representation of environmental factors potentially affecting pyrethroid resistance mechanisms in mosquitoes. Insecticide-based selection pressures are shown as red arrows. Other factors potentially affecting resistance mechanisms are shown in grey (pollutants), orange (non-pesticide agrochemicals), green (plant xenobiotics) or blue (microbial interactions).

insensitivity and metabolic resistance (Marcombe et al., 2009a,b). A subsequent study at the population level correlated resistance levels and the expression of particular detoxification genes with agriculture activities (Marcombe et al., 2012).

It is frequently argued that residual insecticides from agriculture found in mosquito breeding sites may not reach sufficient environmental levels, as to be lethal to mosquitoes, and thus would not select for resistance. However, synergistic and additive effects between insecticides is a well-known phenomenon that can lead to toxic effect of cocktail molecules whereas the very same compounds considered individually are not lethal (Ahmad and Hollingworth, 2004; Ahmad et al., 2009; Niu et al., 2012; Waliwitiya et al., 2012).

In addition to pesticides and insecticides, chemicals commonly used in agriculture also include fertilizers, herbicides, fungicides and various adjuvants that increase their efficiency. Although these compounds are usually non-toxic to insects, their presence in breeding sites has been shown to affect tolerance to insecticides *via* the modulation of their detoxification system. For instance, *Chironomus tentans* larvae exposed to the herbicide alachlor respond by enhanced GST activities (Li et al., 2009). *Ae. albopictus* larvae exposed for 48 h to the fungicides triadimefon, diniconazole and pentachlorophenol showed an increased tolerance to carbaryl (Suwanchaichinda and Brattsten, 2001). The strong effect observed with pentachlorophenol was further linked to a strong induction of P450s. Poupardin et al. (2008, 2010) demonstrated that exposing *Ae. aegypti* larvae to a sub-lethal dose of copper sulphate, frequently used in agriculture as a fungicide, enhance their tolerance to the pyrethroid permethrin. This effect was correlated to an elevation of P450 activities and the induction of CYP genes preferentially transcribed in detoxification tissues and showing high homology to known pyrethroid metabolizers. Similarly, exposing *Ae. aegypti* larvae to the herbicide glyphosate, the active molecule of Roundup, led to a significant increase of their tolerance to permethrin together with the induction of multiple detoxification genes (Riaz et al., 2009). Cross-effects of the herbicide atrazine, copper sulphate and insecticides were further investigated at the transcriptome scale by high throughput cDNA sequencing. This study confirmed their impact on the expression of detoxification enzymes but also evidenced transcription variations in cuticular proteins, transporters and other enzymes families (David et al., 2010). Safeners are used in agriculture to protect non-target crops against herbicides. To date, the effect of these chemicals on mosquitoes remains unknown. Theoretically, safeners can interact directly with herbicide target, alter its uptake or translocation, or increase its degradation (Davies, 2001). In fact, most safeners act as strong inducers of crop detoxifying enzymes, such as P450s and GSTs (Davies and Caseley, 1999). As most known detoxification enzyme inducers have shown effectiveness in insects (Enayati et al., 2005; Feyereisen, 2012), the impact of plant safeners on the potential enhanced metabolic responses of mosquitoes to pyrethroids requires further attention.

4. Impact of urban and industrial pollution

Urbanization is an exponentially growing process in developing countries due to rural exodus for employment prospect, which lead to temporary housing facilities, low access to health care and proper water supply in addition to the increase of vector-borne diseases such as malaria (Caldas de Castro et al., 2004; Keiser et al., 2004). Indeed, multiple suitable man-made breeding sites could be produced in urbanized areas, facilitating the invasion and establishment mosquito populations in proximity to their hosts. In most African urban areas, insecticides are used for domestic purposes, including the control of mosquitoes in the form of mosquito coils, fumigation bombs or sprays (Elissa et al., 1993). These insecticides are used in an uncontrolled and heterogeneous manner in term of coverage and doses of insecticides in each household. Such practices may represent an additional selective pressure favouring pyrethroid resistance in urban areas. Such potential side effect of urbanization was suggested by Diabate et al. (2002) in *An. gambiae* from Burkina Faso where urban mosquito populations were more resistant to DDT and pyrethroids. However, adults used for insecticide susceptibility tests in this study were obtained from larvae collected in the field, which may have experienced different chemical challenges affecting their susceptibility to insecticides.

Indeed, rapid urbanization is always associated with increased pollution. Pollutants generated by traffic, industries, petroleum refinement and domestic wastes can accumulate at high concentrations in the city atmosphere, as well as in rivers and ponds where they are dissolved or adsorbed to organic matter particles. Common pollutants found in urban water bodies include polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), dioxins, heavy metals (Fe, Pb, Cd, Hg …) or human drugs, such as contraceptives (hormone analogues) and painkillers (Buchberger, 2007). As for agriculture, urban pollutants are always found in mixtures whose contents vary in time and space, and are often not toxic (taken individually) to mosquitoes at environmental doses. However, several of these chemicals have been shown to affect mosquito detoxification enzymes and their response to pyrethroids. For instance, exposing *Ae. albopictus* larvae to benzothiazole, a major leachate compound of automobile tires, increased their tolerance to various insecticides. Such effect was linked to an induction of P450 activity (Suwanchaichinda and Brattsten, 2002). Similarly, exposing *Ae. aegypti* larvae for 24 h to a sub-lethal dose of the PAH fluoranthene increased their tolerance to permethrin and induced GST and P450 activities. Microarray and RT-qPCR analyses revealed that such effect was correlated to the induction of several CYP genes including candidates linked to pyrethroid metabolism (Poupardin et al., 2008, 2010). A similar study with benzo[a]pyrene confirmed the enhancing effect of PAHs on the tolerance of mosquitoes to pyrethroids linked to an induction of detoxification genes (Riaz et al., 2009). In Nigeria, Djouaka et al. (2007) collected *An. gambiae* larvae from various breeding sites and assessed their resistance status to permethrin at the adult stage. Individuals collected from oily breeding sites were significantly more tolerant to permethrin compared to non-polluted derived mosquitoes. A subsequent study comparing resistance levels and expression profiles of detoxification genes between *An. gambiae* populations from Nigeria and Benin identified multiple detoxification genes over-transcribed in mosquito populations breeding in an oil-spillage area (Djouaka et al., 2008).

Although these studies indicate that urban pollutants can transiently affect mosquito detoxification system leading to a better tolerance to insecticides, the impact of those chemicals on the selection of inherited resistance remains unclear. A study showed that high dose of petroleum products can be toxic by contact to *An. gambiae* larvae, and proposed that the presence of those chemicals in highly polluted environments may cross-select for pyrethroid resistance (Djouaka et al., 2007). Nonetheless, most urban pollutants are not toxic *per se*, and one could argue that they might not directly select for resistance in natural settings. However, they may still tune the selection of resistance *via* the modulation of the expression of mosquito detoxification enzymes, which could affect survival to insecticides and favour the selection of particular genes or alleles. Answering such question solely based on correlating environmental settings and mosquito resistance levels is clearly difficult, since several confounding factors may occur in the field. To overcome these limitations, a laboratory experiment combining *Ae.*

aegypti larvae exposure to a sub-lethal dose of the PAH fluoranthene and their subsequent artificial selection with a lethal dose of permethrin, was performed across several generations (Poupardin et al., 2012). Although 10 generations of this selection regime did not appear sufficient for revealing a significant impact of the pollutant on insecticide resistance levels, more genes encoding detoxification enzymes were found differentially transcribed in the strain exposed to the PAH prior to permethrin selection, demonstrating that the presence of urban pollutants can modulate the selection of mosquito detoxification genes.

5. Impact of natural xenobiotics

Plants have developed various mechanisms to protect themselves against competitors and herbivores. Among them, the production of allelochemicals, such as alkaloids, cyanogenic glycosides, coumarins, terpenoids, phenolic compounds or tannins play a central role in their defence against insects (Despres et al., 2007). Plant chemicals are known for their insecticide properties for centuries, and were later used to develop diverse synthetic insecticides, including pyrethroids (Casida and Quistad, 1998; Shaalan et al., 2005; Tomizawa and Casida, 2005). Decades of research on botanical insecticides confirmed that multiple plant extracts containing various compounds are toxic to mosquitoes (Shaalan et al., 2005). In response to plant chemical defences, insects have evolved various adaptive strategies, including the diversification of their detoxification systems (Berenbaum, 2002; Li et al., 2007). Such highly diversified detoxification toolbox represents the evolutionary basis of metabolic resistance mechanisms of mosquitoes to chemical insecticides (Despres et al., 2007).

Considering that mosquito breeding sites often contain dissolved plant chemicals or plant particles from which larvae may feed on, the question of the relative impact of these natural xenobiotics on the response of mosquitoes to pyrethroids is pertinent (Kim and Muturi, 2012). Their presence may temporarily affect mosquito metabolism, modulating their tolerance to insecticides. In addition, plant-derived toxic compounds constantly present in mosquito breeding sites might cross-select resistance mechanisms to pyrethroids. Currently, little is known about the role of plant chemicals in mosquito response to pyrethroids; however, studies conducted in other insects suggest that cross-effects may occur in mosquitoes. For instance, after exposing larvae of the corn earworm *Helicoverpa zea* to the furanocoumarin xanthotoxin, survivors and their offspring displayed higher tolerance to the pyrethroid α-cypermethrin, suggesting that this increased resistance is heritable (Li et al., 2000). Moreover, *H. zea* larvae fed with diet containing flavone, β-naphtoflavone or rutin showed a better survival after various insecticide treatments, including α-cypermethrin (Wen et al., 2009; Yu, 1983, 1984). In the fall armyworm *Spodoptera frugiperda*, larvae fed on various host plants and allelochemicals showed increased GST and P450 activities affecting their tolerance to insecticides (Yu, 1983, 1984). In mosquitoes, synergistic or antagonistic effects between plant extracts and chemical insecticides, including pyrethroids, have been described (Shaalan et al., 2005). Feeding *Ae. aegypti* larvae with polyphenol-rich leaf litter particles led to the induction of global P450 activity, supporting the impact of plant compounds on mosquito detoxification system (David et al., 2006). Interactions between plant chemicals and metabolic response to pyrethroids are also supported by the fact that insect P450s frequently linked to pyrethroid resistance, are often induced by or capable of metabolizing plant compounds (Chiu et al., 2008; Li et al., 2004, 2007; McLaughlin et al., 2008; Sasabe et al., 2004). However, some plant chemicals may also repress the expression of particular detoxification enzymes involved in resistance (Yu and Abo-Elghar, 2000; Yu and Huang, 2000). In consequence, the impact of plant compound mixtures found in natural environments on mosquito response to insecticides remains barely predictable until more data are acquired on this subject.

6. Impact of microbial agents

Mosquitoes sustain with varying degree of susceptibility to infections with human pathogens, such as the malaria parasite, viruses or worms. In addition, as other insects, mosquitoes harbour a wide range of microorganisms (*i.e.* microbiome) from pathogens to symbionts which may have variable impacts on mosquito life traits.

Transcriptomic studies focussing on detoxification genes in *An. gambiae* pointed out global gene regulation in response to infection with the malaria parasite *Plasmodium* (Félix et al., 2010). Notably, the gene encoding the cytochrome P450 CYP6M2, capable of metabolizing pyrethroids, was up-regulated in the mosquito midgut when parasites breached through the intestinal epithelium (Félix et al., 2010; Stevenson et al., 2011). In *Cx. pipiens*, intensity of the intracellular bacterium *Wolbachia* infection was higher in resistant mosquito strains, suggesting a cost of infection that negatively relates to insecticide resistance status. Resources allocated to controlling *Wolbachia* proliferation, may be depleted towards insecticide resistance, explaining the increased *Wolbachia* infection in resistant *Culex* strains (Duron et al., 2006; Echaubard et al., 2010; Vidau et al., 2011). In agreement with resource allocations, exposing the honeybee *Apis mellifera* to fipronil and thiacloprid led to higher mortality rates when insects were infected with the microsporidian *Nosema ceranae* (Vidau et al., 2011). As opposed to *Cx. pipiens*–*Wolbachia* system, the development of the filarial worm *Wuchereria bancrofti* in *Cx. quinquefasciatus* is compromised in esterase-mediated insecticide resistant strains, linking higher redox metabolism that impair worm progression in the mosquito host (McCarroll et al., 2000).

The resident gut microbial flora of mosquitoes is known to have significant impacts on the life history of the host such as *Plasmodium* or virus development (Boissiere et al., 2012; Cirimotich et al., 2011; Dong et al., 2009; Meister et al., 2009; Ramirez et al., 2012). However, no studies have yet been published on the relationship between insecticide resistance status of mosquitoes and their microbial flora. A recent study revealed a novel insecticide resistance mechanism through the acquisition by the host of bacteria able to catabolize insecticides (Kikuchi et al., 2012). In this study, infection with an insecticide-degrading *Burkholderia* bacterial symbiont was shown to establish insecticide resistance in the pest insect, *Riptortus pedestris*. In addition, insecticide application in the field massively enriched soils with the insecticide-degrading bacteria, favouring symbiosis and subsequent insecticide tolerance to occur in host insects (Kikuchi et al., 2012). Whether microbial symbionts of disease vector mosquitoes play a role in insecticide resistance is unknown, but answering this question may reveal novel unforeseen avenues of research relevant to the control of mosquitoes and pathogens they transmit.

7. Conclusions

The control of mosquitoes relies largely on the use of chemical insecticides. Pyrethroids play a central role in control programmes, mainly targeting adult mosquitoes. However, the efficacy of such interventions is now threatened by the rapid spread of resistance worldwide in addition to the lack of new approved insecticide molecules. In this context, limiting pyrethroid resistance is of crucial importance for prolonging their efficacy. Improving resistance management involves a better understanding of resistance

mechanisms and environmental factors potentially affecting these mechanisms in a context of increased urbanization and sustainable development.

Although remarkable progresses have been achieved in the identification of genes and proteins linked to pyrethroid resistance in mosquitoes, the picture is far from complete. Additional research efforts are required in several fields such as the functional validation of genes linked to resistance, the relative importance of target-site mutations versus metabolic mechanisms and the selection of particular detoxification enzyme alleles leading to enhanced insecticide degradation.

A better understanding of environmental factors affecting mosquito response to pyrethroid also represents a way to better manage resistance. Among those factors, the use of insecticides in agriculture represents an important selective force likely to affect all types of pyrethroid resistance mechanisms. Although such impact has been suggested by various field studies associating resistance levels with agriculture, additional laboratory and field experiments will allow the validation of the impact of agricultural practices on mosquito resistance and a more precise estimation of the relative importance of this selection pressure compared to insecticides used for vector control.

The presence of other agrochemicals, urban or industrial pollutants and plant compounds in mosquito breeding sites are expected to affect pyrethroid tolerance by modulating mosquito detoxification systems. Enhanced insecticide tolerance has been characterized in the laboratory on individual pollutants. However, quantifying the weight of these xenobiotics in conferring insecticide resistance of field mosquito populations, where pollutants are represented as complex heterogeneous mixtures remains challenging. In addition, although significant effects have been described in mosquito larvae exposed to various xenobiotics, how these phenotypic changes are prolonged at the adult stage, mainly targeted by pyrethroids needs to be further investigated. Understanding how anthropogenic and natural xenobiotics in contact with mosquitoes can affect the selection of inherited pyrethroid resistance is an even more complex issue, but will represent a significant step forward for predicting the dynamics of resistance in diverse environments. Finally, the impact of the diversity and dynamics of mosquito microbiomes on insecticide resistance remains largely unknown and represents interesting research perspectives.

The global emergence of insecticide resistance has frequently been linked in an exclusive manner to the intense selection of mosquito populations by insecticides used for their control. Enlarging this view to consider interactions between mosquitoes and their abiotic and biotic environments may provide unforeseen perspectives for controlling mosquito populations and developing innovative insecticide resistance management strategies.

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