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

Theresia Estomih Nkya [a,b,1], Idir Akhouayri [b,1], William Kisinza [a], Jean-Philippe David [b,*]

[a] National Institute of Medical Research of Tanzania, Amani Medical Research Centre, P. O. Box 81, Muheza, Tanga, Tanzania
[b] Laboratoire d'Ecologie Alpine (LECA), UMR CNRS-Université de Grenoble 5553, Domaine Universitaire de Saint-Martin d'Hères, 2233, rue de la piscine, Bât D Biologie, BP 53, 38041 Grenoble Cedex 9, France

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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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[*] Corresponding author. Tel.: +33 (0) 4 76 51 44 59; fax: +33 (0) 4 76 51 44 63.
E-mail address: jean-philippe.david@ujf-grenoble.fr (J.-P. David).
[1] Both authors contributed equally to this work.

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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 para-type 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

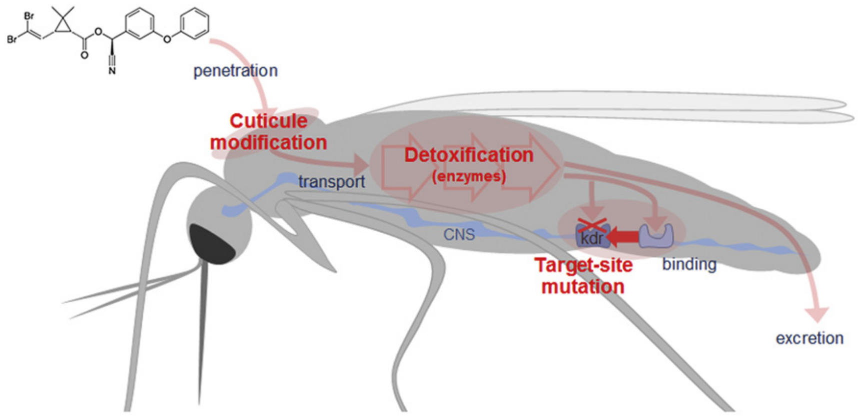

Fig. 1. Main toxicity steps of pyrethroid insecticides and associated resistance mechanisms in mosquitoes. CNS: central nervous system. The pyrethroid molecule represented is deltamethrin.