

Mechanisms of Acaricide Resistance in Ticks

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ABSTRACT

Background: In several countries, including Brazil, the livestock industry plays a key role in the country's economy. Brazil has the second largest bovine herd in the world and the biggest commercial herd. Ticks are an ongoing problem for both large operation cattle producers and small family farmers. *Rhipicephalus microplus* causes expressive losses in cattle breeding, since it occurs in important beef production zones like South America, Africa, and Oceania. Some of the negative consequences of tick infestation to cattle breeding are anemia, loss in milk and beef production, and transmission of *Babesia bovis* and *B. bigemina*. Significant losses are caused by the cattle tick (*R. microplus*) in several regions of the world, costing around US\$ 3.3 billion per year to the Brazilian livestock industry alone. The tick control methods are mainly based on synthetic acaricides. However, the improvement of current tick control requires the identification of new molecular targets in tick physiology and development of molecule compounds to target important physiology pathways. The strategies proposed to address this issue are expand the knowledge about the molecules involved in the detoxification of chemicals to enhance the efficacy of the acaricides as well as to develop new compounds for chemical control.

Review: Tick control is currently based on chemical acaricides; however, effective control and prevention of tick infestation remain distant goals. In recent decades, a progressive decrease in the efficiency of acaricides due to drug resistance has been observed. Acaricide resistance is an evolutionary adaptation, which implies the existence of behavioral and physiological mechanisms that allow the survival of resistant individuals. Four resistance mechanisms are described: behavioral resistance, reduced drug penetration, target site insensitivity and increased drug detoxification. Augmented drug detoxification may be due to increased activity of enzymes or transporters due to increased gene expression or mutations in some genes. Research focus on mechanisms of acaricide resistance in ticks characterized detoxification pathways based on (1) increased activity of enzymes (cytochrome p450, esterase and GST) which play a role in biochemically altering acaricides towards decreased toxicity and, (2) enhanced excretion of the modified less toxic compounds. To bypass the current problems, a better understanding of the biology, physiology, and molecular biology of the mechanisms of resistance to acaricides is fundamental to prolong their efficiency in controlling ticks. Moreover, identifying the genes and proteins associated with resistance can support in the development of more sensitive diagnostic methods to identify acaricide resistance, as well as improving control strategies.

Discussion: In the last years, many researchers have been studying resistance mechanisms and important advances have been made which showed that, in several tick species, ABC transporters, esterases, P-450 cytochromes and glutathione-S-transferases participate in acaricide resistance. The characterization of the alterations in the targets in tick physiology and identification of new drugs with potential to tick control are crucial goals to increase tick control.

Keywords: esterases, glutathione S transferases, pyrethroids, organophosphate, acaricide, resistance, parasite, *Rhipicephalus microplus*, bovine.

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IV. CONCLUSIONS**I. INTRODUCTION**

Ticks are ectoparasites worldwide distributed that infest a variety of vertebrate hosts, presenting a hematophagous behavior and could affect the animal and human health [37,38,126]. The parasitism caused by the cattle tick, *Rhipicephalus microplus*, and the transmission of *Babesia bovis* and *B. bigemina* could lead to host anemia and, consequently, decrease in milk and meat production, with economic annual losses for livestock production reaching US\$ 3.2 billion in Brazil [59,72].

Currently, there are 7 classes of commercially available pesticides to control ticks' infestation: organophosphates, synthetic pyrethroids, macrocyclic lactones, formamidines, benzoylphenyl ureas, phenylpyrazoles and isoxazolines [110,118]. The main targets of pesticides are present in the central nervous system of arthropods having neurotoxic activity [99]. Most of them have a role on ion channels, like Gamma-aminobutyric acid gated chloride channel (GABA-Cl), glutamate-gated chloride channel (Glu-Cl) [13-15,91] and voltage-sensitive sodium channels (Na⁺) [80], acetylcholinesterase enzyme [19,20] and arthropod octopamine receptors (AOR) [49,50]. However, there is an increasing global concern about tick acaricide resistance, since the application of chemical acaricides, over the years, has led to an increase in the reports of resistant populations to these compounds [71], including multiresistant populations to all commercial acaricides in different countries [52,61,76,107,110,134]. In Brazil, a field population of *R. microplus* has already been identified as resistant to 6 acaricides (cypermethrin, chlorpyrifos, fipronil, amitraz, ivermectin and fluzaron) that belong to different classes [107], also

resistance to deltamethrin, fipronil and ivermectin was reported in the brown dog tick, *Rhipicephalus sanguineus* [10].

Until now, 3 main factors have been identified to contribute to resistance selection: cuticle thickening (reducing or delaying the pesticide penetration) [117], target-site insensitivity [22] and detoxification pathways [84], but in ticks the studies are focused on last two. Thus, knowledge and understanding of tick metabolism and the target pathways that contribute resistance selection can help in the identification of new targets, as well as in the development of novel control strategies to overcome increasing resistance to pesticides.

II. TARGET-SITE INSENSITIVITY**1. Voltage channels**

Voltage-gated Na⁺ and K⁺ channels are responsible for the generation of action potentials in neurons and propagation of electrical signals [140]. In ticks, the synganglion, a mass of fused nerves, is the central nervous system, [108] and is an important target of the current acaricides [111]. However, multiple studies revealed that acaricide resistance occurs in many different species of arthropods, including ticks [25,61,97,139]. Acaricide resistance can be determined by different mechanisms, including the metabolic inactivation or degradation of the active molecule. However, most of the times, acaricide resistance is caused by changes in the drug targets [27,45,113]. The concept of drug resistance was first considered when mosquitoes and housefly became resistant to DDT in Italy in 1946 [62].

Pyrethroids are broad-spectrum acaricides and their major mode of action is via interactions with the voltage-gated sodium channel [125]. Mutation mediated knockdown resistance (kdr) is the most common and a frequent cause of resistance to pyrethroids in ticks [22,31]. Several studies on ticks, especially *R. microplus*, have documented several point mutations in the sodium channel associated with reduce sensitivity to pyrethroids [1,21,31,77,127]. Gamma-aminobutyric acid gated chloride channel (GABA-Cl) and glutamate-gated chloride channels (Glu-Cl) are other essential players in the central nervous system functions [124,138,145]. GABA-Cl are targets for several pesticides, including fipronil, lindane and cyclodienes and the novel acaricide class of isoxazolines [22,142,146].

The hyperexcitation caused by antagonist drugs blocks the GABA current leading to arthropod death [142]. Interestingly, fipronil and fipronil sulfone were reported as inhibitors of both channels, GABA-Cl and Glu-Cl [143,144]. The Glu-Cl channel receptors are part of ion channel protein superfamily detected in invertebrates, but not in vertebrates [26], and appears to be the target of macrocyclic lactones in *Caenorhabditis elegans*, and in *Drosophila melanogaster*, potentiating the glutamate activated current [33,34]. On the other hand, it was not identified cross-resistance between fipronil and ivermectin in *R. microplus*, suggesting that these acaricides do not present the same target-site [23].

Resistance to dieldrin gene (*rdl*) from *Drosophila* was the first member of GABA-Cl channel genes described in invertebrates [53]. In ticks, it was shown that GABA current was blocked when fipronil was administrated in *Xenopus* oocytes that expressed *rdl* gene from *Dermacentor variabilis*, suggesting a role of this pesticide as blocking the opening of GABA-Cl channels and indicate a potential target to tick control [145]. It was identified that ala to glycine (*gly*) substitution in *Anopheles gambiae* *rdl* locus for GABA receptor conferred resistance to dieldrin [43]. Also, mutations in GABA-Cl gene led to dieldrin and fipronil resistance in *R. microplus* [22,70]. However, a study showed that no significant association was found between presence of *rdl* mutations and fipronil resistant phenotypes in cattle tick isolates from Uruguay and Argentina [21,115]. Meanwhile, point mutations in Glu-Cl gene which led to the substitution from alanine (*ala*) to valine (*val*) and from *gly* to aspartic acid (*asp*) were identified in *Plutella xilostella* and *Tetranychus urticae* resistant to abamectin, respectively, both modifications promote a change in the channel conformation interfering with binding of this pesticide to the channel receptor [81,137], but in ticks this resistance mechanism is still unknown.

2. Acetylcholinesterase

The acetylcholinesterase is a serine hydrolase that degrade acetylcholine and terminate neurotransmission [93]. However, tick exposition to organophosphate acaricides result in inhibition of cholinesterase, so acetylcholine accumulates at the cholinergic synapse, keeping the receptors activated causing paralysis and death of tick [54].

In *R. microplus*, single nucleotide polymorphism in 2 acetylcholinesterase genes (*AchE1* and

AchE3) has been associate to organophosphates resistance [11,133] since the mutation is present in *R. microplus* resistant strains [132]. Interesting, it was observed that in insects and ticks multiple simultaneous mutations can occur in the same acetylcholinesterase gene increasing the level of resistance [54,75,88,92,104].

Amitraz belongs to another class of acaricides that is extensively used for tick control, but resistance to this pesticide have been detected since the 1990's [73]. In the same way of organophosphates, there are still questions about the mechanisms involved in amitraz resistance.

3. Octopamine receptors

Formamidines are a class of acaricides that act as agonists by stimulating the octopamine receptors (AOR), the consequence is a decrease in intracellular Ca^{2+} and activation of K^{+} efflux leading to interruption of nervous transmission and death [7,49,96]. These pesticides have a role mainly against the β AOR, despite the arthropods have 3 AOR: α -adrenergic-like octopamine receptors (α AOR), octopamine/tyramine receptors (OCT/TYR) and β -adrenergic-like octopamine receptors (β AOR) [29,50,63,95]. In addition, formamidines have also been shown to interfere in octopamine / tyramine receptors activated [60].

Therefore, although OCT/TYR gene has been sequenced in *Rhipicephalus australis* from Australia, mutations in these sequences from susceptible and resistant strains to amitraz were not initially identified in that country, suggesting that other pathways could be involved in this pesticide resistance [9]. However, posteriorly, point mutations in OCT/TYR sequences related to amitraz resistance were detected in resistant ticks from Brazil, Mexico, South Africa, Zimbabwe and India [4,22,24,109,129]. Also, the intragenic recombination of OCT/TYR could be suggested as important in the emergence of resistant populations [8]. Another work associated non-synonymous mutations (from *ile* to *phe*) in β AOR sequence from *R. microplus* to amitraz resistance, but not all resistant populations presented this genotype, suggesting the involvement of other mechanisms in resistance pathway [28,73], but this mutation was confirmed to reduce the effect of N2-(2,4-dimethylphenyl)-N1-methylformamidine, an amitraz metabolite, in *Bombyx mori* and their resistance potential needs to be confirmed in ticks [130].

III. DETOXIFYING PROTEINS AND DETOXIFICATION PATHWAYS

The best-known mechanism in acaricide-resistant ticks is the metabolic detoxification [30,39,113]. This pathway is characterized by increased activity of enzymes, such as esterase (phase I), cytochrome P450 (CYP450) (phase I) and glutathione S-transferase (GST) (phase II) [2], playing a role in modifying acaricides toward decreased toxicity, forming more hydrophilic molecules and enhancing excretion of the less toxic compounds out of the cells (phase III) [103].

1. Esterases

Two beta-carboxylesterases (serine hydrolases) sequences were identified in *R. microplus* and a point mutation (G1120A) was found in one of these genes from pyrethroid resistant Mexican strains [64,68]. Carboxylesterases have a role in pesticide detoxification and besides the presence of mutations in their sequence, an overexpression of these enzymes has also been described in other arthropods, like *Musca domestica* [51]. In ticks, an increased hydrolysis capacity of carboxylesterase was detected in *R. microplus* resistant to the organophosphate coumaphos, which is possibly associated to resistance to this pesticide [135]. Increased activity of alpha- and beta-carboxylesterases was also shown in *R. microplus* larvae resistant to fluazuron [56]. Meanwhile, another study analyzed the transcription level of an esterase gene in 2 pyrethroid resistant tick strains. In 1 strain, a higher number of transcripts was observed in larvae and in the hemolymph collected from resistant engorged females, in comparison to pyrethroid-susceptible ticks. However, in the second strain no differences were observed in the expression of the esterase encoding gene in relation to susceptible ticks. Therefore, these results suggest that different pathways can contribute to resistance to the same acaricide [67].

2. Cytochromes P450

Cytochromes P450 metabolize xenobiotics, being a common detoxification mechanism in several arthropod species, and has also been linked to pyrethroid resistance in insects and other arthropods [69]. In several arthropods, CYP450-mediated resistance is characterized by the gene overtranscription, resulting from alterations in the factors that regulate its expression [86,116]. In the red flour beetle, *Tribolium castaneum*, populations resistant to phosphine

showed increased susceptibility to this pesticide when a CYP450 inhibitor (piperonyl butoxide - PBO) was used. Also, a significant up-regulation of CYP346B subfamily genes was described in this resistant insect species [136]. In *Drosophila melanogaster* lineages over-expressing *CYP6G1*, *CYP6G2* and *CYP12D1*, increased survival to insecticides DDT, nitenpyram, dicyclanil and diazinon was detected [35]. In *A. gambiae* a CYP450 enzyme was located in oenocytes and it is related to hydrocarbon production, which leads to the thickening of the cuticle of pyrethroids-resistant mosquitoes and consequently insecticide uptake reduction [6]. Also, in *R. microplus*, a proportional increase in transcription of CYP450 was identified in pyrethroids-resistant populations [30]. Similar results were described in *R. sanguineus sensu lato*, since when PBO was used in synergist bioassay, an increase in tick mortality was shown, restoring the permethrin toxicity in pyrethroid-resistant isolates, indicating a role of CYP450 in metabolic detoxification. However, the same pattern has not been described in fipronil-resistant populations, suggesting that another mechanism may be involved in this resistance pathway [46]. In contrast, some CYP450-encoding genes presented decreased transcripts levels, while other CYP450 genes were over transcribed when *R. microplus* resistant to pyrethroids were exposed to deltamethrin. This could be explained by the need of the high transcription of genes necessary for survival post-acaricide treatment [94].

The exposure to PBO slightly increased (1.4-fold) amitraz toxicity in susceptible *R. microplus*, however, the synergistic effect of PBO was significantly increased (2.9-fold) in an amitraz-resistant isolate, suggesting a role of P450s in resistance to the formamidine in cattle ticks [82].

Besides their detoxification role, CYP450 can also act in metabolization and consequent activation and enhancement of the pesticide toxicity, like organophosphates. It was observed that CYP450 activity was reduced in organophosphate-resistant tobacco budworm (*Heliothis virescens*) [78]. The use of PBO decreased the coumaphos toxicity in acaricide-susceptible *R. microplus*, while synergistic effect was shown in resistant isolates, however, the same synergic activity with diazinon was not identified when PBO was used in resistant isolates [85]. On the other hand, it was not detected significantly differences in the CYP450 gene expression levels in organophosphate-resistant and

susceptible *R. microplus*, suggesting a multifactorial resistance mechanism to this acaricide [32].

3. Glutathione S-transferase

The tick GST catalyzes the conjugation of reduced glutathione (GSH) with a wide variety of endogenous and exogenous electrophilic compounds, protecting the cell from oxidative damage [3]. Thus, this enzyme could have a role in the tick resistance to acaricide. While GST enzyme overexpression is frequently associated with drug resistance [10], reports on the participation in acaricide resistant ticks are sparse. However, there is data of increased GST transcription in acaricide resistant tick populations [55,66]. Excitingly, GST-gene RNAi silencing is shown to induce acaricide susceptibility in ticks [44]. Currently, 7 classes of these enzymes are known in mammals, named Alpha, Mu, Pi, Sigma, Theta, Zeta and Omega, according to their chromosomal location [119]. In insects, Delta and Epsilon classes are also present, and are implicated in *Anopheles gambiae* detoxification pathways [105,106]. GST enzymes are subdivided in cytosolic, microsomal, and mitochondrial (Kappa) categories [120], however the last one was not identified in insects so far, but are present in other arthropods, like crustaceans [112]. In insects, cytosolic class are subdivided in Delta, Epsilon, Omega, Theta, Sigma and Zeta [47]. In *Tribolium castaneum*, 36 putative cytosolic GSTs and 5 microsomal GSTs were identified, while in *Bombyx mori*, only 23 cytosolic GSTs were observed, it is interesting to highlight that the class which contains the highest number of detected sequences was the *Epsilon* for both insect species [121,141], also in *Drosophila* the main classes are Epsilon followed by Delta [58]. These cytosolic enzymes act by catalyzing the conjugation to glutathione (GSH), facilitating that more hydrophilic substrate to be transported out of the cell [120]. In *Tenebrio molitor*, it was hypothesized that cytosolic GSTs act by sequestration and binding to the pyrethroids, thus allowing the detoxification process. However, no relationship was found between GSH concentration and resistance to insecticides [79]. High transcript levels of Delta GST were found in *D. melanogaster* chemosensory organs, after isothiocyanate exposition. This enzyme was over transcribed, suggesting an insecticide protection role [58].

Also, in *Haemaphysalis longicornis*, 2 GSTs-encoding gene transcripts were identified in several organs of larvae, nymph and adults, it is interesting to

note that during blood feeding, higher transcript levels were observed, however protein levels decrease after engorgement, moreover location of GST in midgut and salivary glands depends on the feeding, and GST may be related to oxidative stress [66]. The expression of this enzyme is induced by heme, not by iron present in the blood, thereby reducing the cytotoxic effects caused by blood components [100]. Recombinant GSTs (rGSTs) from *H. longicornis* and *Rhipicephalus appendiculatus* had their activity inhibited by acaricides [123]. Similar effects were observed rGST from *R. microplus* using different acaricides. However, coumaphos shown to increase rGST activation, suggesting different interaction mechanisms between acaricide and detoxification enzymes [122]. Furthermore, increasing flumethrin doses led to increase of GST gene transcription in tick males, while GST knockdown decreased the larval survival rate after acaricide treatment [65], accordingly, permethrin has been shown to have more toxic effects on *R. sanguineus sensu lato* knockdown for GST, thus suggesting this protein as an alternative control target for ticks [44]. Natural compounds [12,89,131] or synthetic molecules [98] can alter GST activities and can consequently lead to the improvement and development of new acaricides.

4. ABC transporters

Lastly, P-glycoproteins (P-gps) are ABC transporters that influence drug uptake and excretion, interacting with different agents and have been related as a protection mechanism against pesticide in mosquitoes, including a multidrug resistance pathway, may be the first line of defense of cells [5,17,36,57,74]. Nevertheless, ABC transporters are poorly understood in arthropods and only some species present a characterization of putative ABC genes. These were grouped into 8 families (from ABCA to ABCH), in *Tribolium castaneum*, *Tetranychus urticae*, *Bombyx mori*, *Anopheles gambiae*, *Daphnia pulex* and *Drosophila melanogaster* [16,40,42,87,114,128]. In *Anopheles stephensi*, ABCB and ABCG augmented transcription has been associated with permethrin resistance, since when mosquitoes were exposed to ABC inhibitors and to the insecticide an increase in larval mortality was observed. Also, an over-transcription was detected in ABCG-encoding genes when the mosquitos were exposed to permethrin alone, but similar results were not identified for ABCB-encoding genes [48]. In contrast, a *D. melanogaster* lineage knocked-out to homologous

of mammalian ABCB-encoding genes (*Mdr65*) was more susceptible to several insecticides than other genes tested, showing synergistic activity with ABC transporter inhibitor, whereas flies knocked-out to other *Mdr* genes were resistant to some pesticides [41].

Although little is known about these transporters in insects, in ticks the knowledge is even scarcer. The first association between ABC transporters and acaricide resistance was demonstrated in *R. microplus* resistant to ivermectin. The exposure of the ticks to compounds that interfere with ABC proteins (cyclosporin-A) in association with the acaricide treatment, lead to the reduction in oviposition and egg viability of treated engorged female ivermectin-resistant ticks. In addition, a decrease in ivermectin lethal concentration was observed [102]. Similar results were observed in *R. sanguineus sensu lato* (exposed to fipronil and ivermectin) [18] and with a multiple acaricide resistant strain of *R. microplus* (exposed to ivermectin, abamectin, moxidectin and chlorpyrifos) [103], suggesting that ABC transporters could act as a multidrug detoxification mechanism, with the ABC transporters inhibition as an approach for tick control. Interestingly, an up-regulation in the transcription of the ABCB-encoding gene was detected for resistant population (Juarez) exposed or not to ivermectin, the same was not identified for ABCC-encoding gene and for susceptible strain (Porto Alegre) [102]. A cell line from *Ixodes ricinus* exposed to 3 acaricides (amitraz, permethrin, and fipronil) showed differences in up- and down-regulation for ABCB and ABCC-encoding genes depending on the pesticide treatment, showing different pathways and cell responses according to the drugs tested [90]. *In vitro* assays were also performed using ivermectin-resistant *R. microplus* embryonic cell line. An increase in ABCB transcriptional level was observed in resistant cells exposed to acaricide, while the resistance decreased after treatment with ABC transporters inhibitor, demonstrating the role of these transporters in resistance to ivermectin, however once again similar results were not observed

to ABCC [101]. Moreover, an association between amitraz detoxification and heme transportation in midgut was proposed for *R. microplus* ABCB transporters, suggesting that resistance to acaricides may be a consequence of endogenous compound detoxification pathway [83]. Confirming that several physiological mechanisms can act on pesticide resistance, in *Rhipicephalus microplus*, toxicological assays confirmed that esterases and ABC transporters contribute to ivermectin resistance, followed by GSTs and CYP450 [84].

IV. CONCLUSIONS

Ticks and tick-borne diseases are significant impediments to livestock production. Current tick control methods are mainly based on chemical acaricides; however, effective control and prevention of tick infestation remain distant goals. In recent decades, a progressive decrease in the efficiency of acaricides due to drug resistance has been observed. To bypass the current problems, a better understanding of the physiology and molecular biology of the mechanisms of resistance to acaricides is fundamental to prolong their efficiency in controlling ticks, as well as improving control strategies.

This includes, expand the knowledge about the molecules directly involved in the detoxification of chemicals to enhance the efficacy of the acaricides as well as to develop new compounds for chemical control.

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