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Review Article

STATUS OF ACETYLCHOLINESTERASE MEDIATED ORGANOPHOSPHATE RESISTANCE IN CATTLE TICK, *RHIPICEPHALUS MICROPLUS* (ACARI: IXODIDAE)

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ABSTRACT: Ticks, the haematophagus ectoparasites with worldwide distribution especially in tropical and sub-tropical regions, severely affect health and productivity of animals. Different classes of chemical acaricides like organochlorines, organophosphates, formamidines, synthetic pyrethroids and macrocyclic lactones are currently used for controlling the tick infestations. The continuous and indiscriminate treatments often leads to acaricide resistance, environmental pollution and residues in meat and milk products. Organophosphate (OP) compounds were initially introduced as a replacement to organochlorines as they were non-persistent and did not accumulate in the fat tissues. The global scenario of OP resistance development in cattle tick, *Rhipicephalus microplus* has been summarized in the present review. The various resistance mechanisms against OPs in *R. microplus* include target site modification in the acetylcholinesterase (AChE), and carboxylesterase (CE) gene, as well as metabolic detoxification.

Keywords: Acaricide resistance, Acetylcholinesterase, Organophosphate, Cattle tick.

INTRODUCTION

The ticks are significant blood sucking ectoparasites affecting domesticated animals causing serious threat to the livestock industry, especially in tropical and sub-tropical regions. Heavy tick infestations cause severe economic losses directly through anorexia, toxicosis, decreased milk production and weight gain, damage to hide, treatment costs and indirectly by increased mortality due to tick-borne infections. The estimated annual cost of management of tick and tick-borne diseases (TBDs) in livestock globally is US$ 14000-18000 million and of India is US$ 498.7 million [1]. As per a recent report the annual cumulative loss due to infestation of ticks and TBDs is 61076.46 million INR or 787.63 million USD [2].

Presently, control of ticks is predominantly dependent on chemical acaricides, *viz.*, organophosphates (OP), synthetic pyrethroids (SP), formamidines and macrocyclic lactones (ML). Application of these drugs often leads to acaricide resistance, pollution of environment and residues in meat and milk products. The tick resistance to acaricides is inherited and has resulted from exposure of tick populations to chemical acaricides that are less affected by acaricides. The drug resistance mechanisms in ticks are generally because of increased metabolic detoxification and target site insensitivity [3]. The establishment and development of resistance also depends on the frequency of acaricide treatment, use of low doses and poor quality acaricides, frequency of the original gene mutation and mode of inheritance of the resistant allele. Presently, the drug resistance in cattle ticks has been the major challenge in controlling tick infestation in tropical and sub-tropical regions including India. Large populations of *Rhipicephalus microplus* are reported to be resistant to various classes of chemical acaricides.

Organophosphates were introduced around 1950, as a replacement for the organochlorine insecticides which remained persistent in the environment and were prone to accumulation in body fat. The OP compounds are chemically unstable, non-persistent, most toxic of all

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pesticides to vertebrates [4], do not amass in fatty tissues of animals and are highly toxic to humans when compared to organochlorines. Dieldrin, ethion, chlorpyrifos, chlorfenvinphos, diazinon and coumaphos are the widely employed OP to treat the tick-infestation in dairy animals. The OP pesticides cause various adverse impacts on different environmental matrices, animal and human due to their direct exposure and food chain bio-accumulation. They work continuously as they are detected constantly in soil, sediments, water and air [5, 6]. The present review primarily deals with the various important aspects of OP resistance development in cattle tick, *R. microplus*, and may also enlighten resistance development against other classes of acaricides due to their indiscriminate and uncontrolled use.

RESISTANCE AGAINST ORGANOPHOSPHATES

First report of OP resistance in ticks was from Australia in mid-1960s and is currently widespread across all over the world including India (Table 1). Development of OP resistance has minimized their use in many regions of the world.

Table 1. Worldwide reports on OP resistance in Rhipicephalus microplus.

OP acaricide	Country [Reference]
Chlorfenvinphos	Jamaica [7], Colombia [8], Mexico [9], South Africa [10]
Dieldrin	Australia [11-13], Tanzania [14], Mexico [15]
Chlorpyriphos	Australia [13], Brazil [16-21], Costa Rica [22], Mexico [23-24], Colombia [25], New Caledonia [26]
Coumaphos	Australia [13, 20], Mexico [9, 15, 23, 24, 27], Colombia [8], Costa Rica [22], USA [28], Brazil [20], India [29, 30]
Diazinon	Australia [31], Mexico [9, 15, 23, 32], Colombia [8], India [30, 33-41], New Caledonia [26]
Malathion	India [33, 42-45]
Ethion	Mexico [15], Uruguay [46], Australia [47], New Caledonia [26, 47]

ACETYLCHOLINESTERASE: TARGET FOR ORGANOPHOSPHATES

Acetylcholinesterase (AChE), a cholinergic enzyme, is chiefly present at the post-synaptic neuromuscular junctions of nerves and muscles. The AChE breaks down or hydrolyses, the neurotransmitter acetylcholine to acetic acid and choline immediately. The AChE is considered to be target site of OP acaricides. Some OPs may also exert substantial metabolic effects in other pathways also. The AChE enzyme in insect and mammalian systems is one of the fastest enzymes, despite having a catalytic triad buried deep within the protein structure. When cholinesterase inhibitor is given to ticks, the cholinesterase is not available to break down the acetylcholine, and the neurotransmitter continues to cause the neuron to send its electrical charge. Due to this, there is overstimulation of nervous system, ultimately leading to paralysis and death [48].

Tick acetylcholinesterase and OP resistance

Development of OP resistance in ticks is complex, multigenic and include metabolic detoxification and modifications in the target AChEs gene [49]. The metabolic detoxification mechanisms involving enzymes had been reported amongst the principle mechanisms of OP resistance in *R. microplus* [50, 51]. In the course of resistance development, there is structural modification in AChE enzyme, and subsequently, the drugs are unable to act on the resulted altered enzyme [52]. The altered AChE enzyme which was first reported from OP-resistant strain of a spider mite and later in cattle tick [53]. Flies contain only a single AChE gene and mosquitoes have two AChE genes, while the *R. microplus* ticks express three different transcripts encoding AChEs, viz. BmAChE1 [54], BmAChE2 [55], and BmAChE3 [56]. The sequences of amino acids of these three BmAChEs were not closely related to one another than AChEs from different organisms. The biochemical characterization of baculovirus expressed rBmAChE1, rBmAChE2 and rBmAChE3 has been reported [57] .

Metabolic detoxification and OP resistance

This mechanism is considered as one of the principle mechanisms of OP resistance to *R. microplus*. The OPs might interact with esterases in the integument of larval and adult ticks, leading to the over-expression of esterases which leads to resistance [58]. The OP resistance has been reported to occur primarily via conformational and metabolic activities changes in AChE enzyme in resistant ticks [59]. Besides that, post-translational modifications in AChEs proteins are also suggestive of resistance mechanisms [54]. Lee and Batham [60] biochemically characterized the AChE activity extracted from OP-resistant ticks, to be

insensitive to OP inhibition. The Mexican populations of *R. microplus* were shown to possess a target site-mediated resistance to OPs, as reported through esterase-based metabolic hydrolysis of Caumaphos. Jamroz *et al.* [61] employed biochemical analyses for quantification of esterase-based metabolic mechanisms of OP resistance in the Coatzacoalcos, Corrales and Mexican Tuxpan strains of *R. microplus* ticks. A carboxylesterase, Est10, was reported to be more abundant in the coumaphos resistant Tuxpan strain and it was correlated with OP resistance. Villarino *et al.* [62] also detected esterase-based metabolic resistance to OPs in *R. microplus* adult female ticks. Li *et al.* [51] reported coumaphos resistance mechanism in R. microplus (San Roman strain) as both enhanced metabolic detoxification and insensitive AChE. The Brazilian strain of *R. microplus* resistant to malathion had increased levels of AChE in comparison of the susceptible strains [63]. The percent uninhibited activity of AChE in *R. microplus* larvae with propoxur was reported to be positively correlated with a possible role in development of malathion resistance in Punjab field isolates of *R. microplus* [44]. There are reports of involvement of other enzymes, *viz.*, cytochrome P450 and glutathione S-transferase in imparting resistance to OPs.

Molecular mechanism of OP resistance

The molecular mechanisms of OP resistance have been studied widely in different insects. In ticks, the target site of OPs is AChE and *R. microplus* has three different genes, each encoding an enzymatically active AChE. A large number of mutations have been reported in all the three AChEs from all over the world leading to target site insensitivity an important mechanism for development of OP resistance. Models for the molecular mechanism of AChE- resistances are based on the detailed structure-function knowledge of the instensively analysed AChEs from *Drosophila melanogaster*, *Torpedo californica* and *Homo sapiens*. A cartoon structure representation of active site motif is given in Fig. 1.

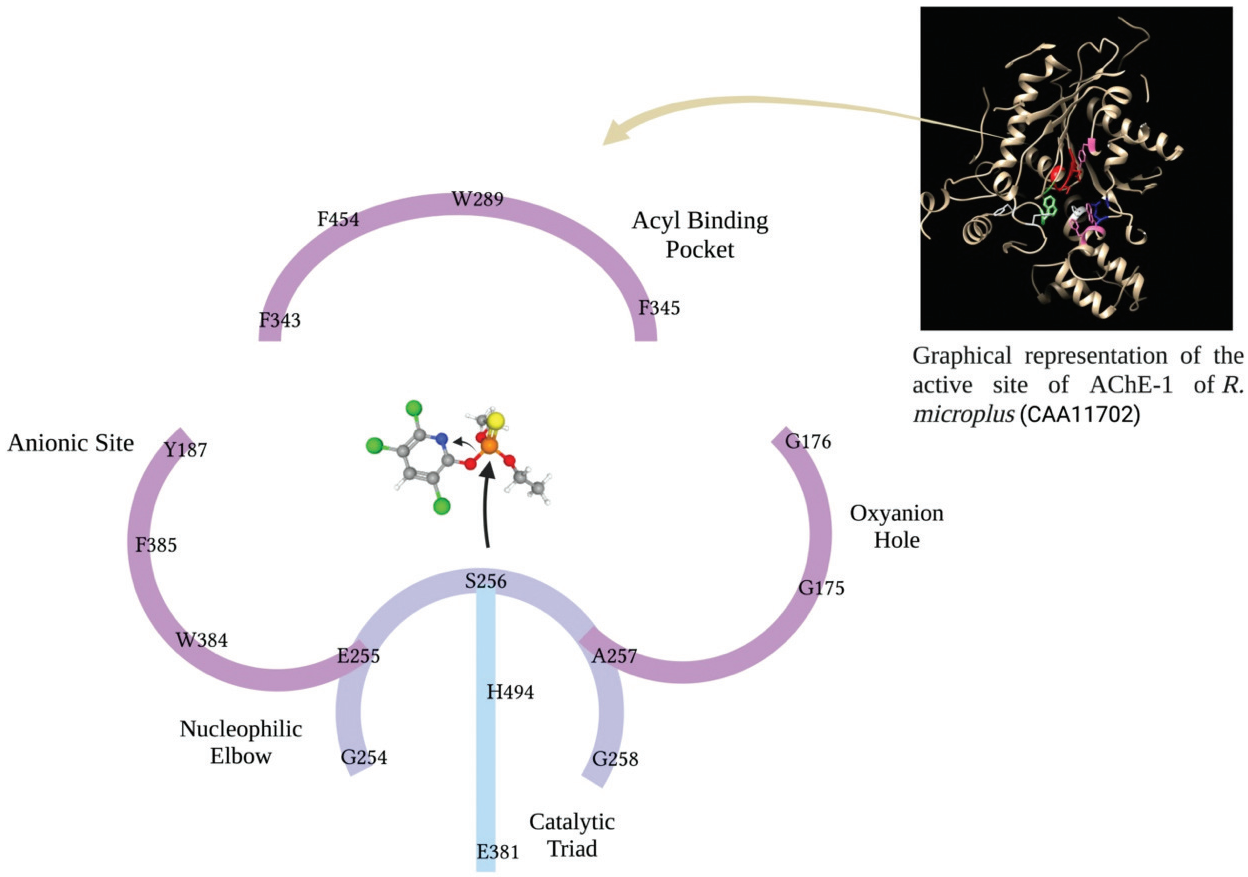

Fig. 1. A schematic representation of the AChE-1 active site occupied by Chlorpyrifos.

Polymorphism in AChE 1 gene associated with OP resistance

Baxter and Barker [54] first identified a cDNA, BmAChE1, in *R. microplus* ticks presumptively encoding AChE and no mutation was found in various tick strains. They suggested that there may be another gene encoding AChE which may be responsible for resistance, or it may result from post-translational modifications of BmAChE1. Temeyer *et al.* [57] constructed a recombinant of AChE1 containing several amino acid substitutions which showed reduction in paraoxon sensitivity compared to that of AChE3 of *R. microplus*. They compared 16 amino acid substitutions to the susceptible type AChE1 sequence, and found D188G, E196G, V331A and F390S substitutions in the paraoxon insensitive construct, and the D188G and F390S were considered to be responsible for the paraoxon insensitivity.

Polymorphism in AChE 2 gene associated with OP resistance

Five SNPs (G138A, G889A, T1090A, C1234T and G1403A) in the AChE2 gene of laboratory-reared *R. microplus* line IVRI-III and OP resistant field populations from Bihar, India were detected by Ghosh *et al.* [37]. G138A was a synonymous mutation, while other four nucleotide substitutions were non-synonymous leading to change in amino-acids, *viz.* V297I (valine for an isoleucine in position 297), S364T (serine for a threonine in position 364), H412Y (histidine for a tyrosine in 412) and R468K (lysine for an arginine in position 468). They suggested that these mutations could be associated with OP resistance but as there was a moderate to high range of resistance in the field collected ticks having these mutations, the actual contribution of these mutations in the development of insensitive AChE2 could not be ascertained. Nagar *et al.* [64] identified the same four non-synonymous amino acid substitutions (V297I, S364T, H412Y and R468K) in AChE2 gene of resistant field populations collected from different agro-climatic regions of India and in reference resistant tick lines of *R. microplus*.

Polymorphism in AChE 3 gene associated with OP resistance

In an OP-resistant San Roman strain of Mexican *R. microplus,* Temeyer *et al.* [48] reported six mutations (I48L, I54V, R86Q, V137I, I492M, and T548A) in BmAChE3. However, none of these mutations alone were sufficient to produce the resistant phenotype because a number of susceptible individuals were found to be homozygous for all the six mutations. The R86Q substitution in BmAChE3 was the first mutation in ticks demonstrated to confer insensitivity to OP, resulting in reduction in paraoxon sensitivity and the presence of it in OP-susceptible strains of *R. microplus* strongly suggests that although this mutation may contribute to resistance development, it alone is insufficient to produce the resistant phenotype. Temeyer *et al.* [65] genotyped the other five mutations and evaluated their frequency and found that these mutations were also present in susceptible strains, suggesting that none of the mutations alone is directly responsible for the insensibility of the AChE enzyme.

Jyoti *et al.* [44] analyzed nucleotide and their deduced amino acids sequences of partial AChE3 gene of *R. microplus* ticks of Punjab, India and found six amino acid substitutions. Among the six substitutions three (I48L, I54V and R86Q) have been earlier reported from OP-resistant San Roman strain of Mexican *R. microplus*, whereas three (V71A, I77M and S79P) were reported for the first time and seem to be unique to Indian ticks. Temeyer *et al.* [66] analyzed the sequence data of AChE1, AChE2 and AChE3 genes of nine susceptible and twenty resistant strains of *R. microplus* and detected amino acid substitutions in these genes of different field strains with variable frequencies but they could not establish their possible association between OP resistance convincingly.

The changes in AChE found to confer terget site resistance in different insects and mites. The site near triad His (F331W, F331F/C); near anionic site (I129V/T); acyl pocket (F290Y) and near oxyanion hole (A201S) mutations were associated with target site resistance in various insects and mites [67]. Recent a molecular models of AChE-1 were generated to know the modified enzyme by resistance-associated mutations in lepidopterous organisms [68]. Similar molecular modling of AChE-1 was geterated to investigate resistance associated mutation in *R. microplus*. Near anionic site (D188G, E195G and E196G); near acyl pocket (F390S); near triad His (I493T) was involved in OP resistance in ticks. All the other substitutions involve changes in the resistance isolates than were present in the susceptible forms. It is generally interpretate due to steric hindarance that limits the access of the OPs to the catalytic site (S256) to which they bind so strongly in susceptible *R. microplus*. The mutations reported by various workers in the AChE genes of *R. microplus* are summarized in Table 2.

Table 2. Mutations in AChE genes of *Rhipicephalus microplus*.

Gene	Amino acid position and substitution	GenBank Accession No.	Association with OP-resistance	References
AChE1	P157S, D188G, E195G, E196G, Y230C, S282G, V331A,T362A, F390S, L417P, Q488R, I493T, P590A, W571R, W571F, N566D	CAA11702	Established	[66]
AChE2	W114R, L141F, K208R, I210V, K555M, M349V, M406V, P343S	AF067771	Established	[66]
	V297I, S364T, H412Y, R468K	-	To be established	[37, 64]
AChE3	I54V, R86Q, I123M, I492M, T548Y, T548A	AY267337	Established	[66]
	I48L, I54V	-	To be established	[65]
	R86Q, V137I, I492M, T548A, V71A, I77M, S79P	KP638388-92; KP713783-85; KP843106-09; KR080147-50; KR827589; KT026442	To be established	[44]

OTHER EFFECTS AND ALTERNATIVE APPROACHES

Transfer of pesticide resistance genes to bring antimicrobial resistance among microorganisms

The OP compounds and many other pesticides can bring various unknown detrimental effects after reaching the environment. They can increase pesticide - degrading organisms of the soil selectively and can give the power of cross resistance to various microorganisms to combat a wide range of antibiotics [69, 70, 71].

Alternative approaches

Control of ticks and mites are important for control of different parasitic diseases. As the development of resistance against the acariides as well as the anti-parasitic drugs [72] is becoming a serious problem day by day, some alternative methods are suggested for control of ectoparasites and the diseases spread by them. Anti-tick vaccine [73], use of herbs [74] to control different parasites, etc. are some important area of study for that purpose.

CONCLUSION

The OP acaricides target AChE critical to tick central nervous system function. Development of phenotypic resistance to OPs in ticks is complex and multigenic. The presence of mutations cannot be correlated conclusively with resistance however, it provides an insight into one of the possible mechanisms operating in OP resistance in *R. microplus* ticks. The cholinesterase gene family in ticks contains a number of related enzymes and structural proteins. This can also imply that other factors exist which contribute to insensitive AChEs other than point mutations. The functional complementarity of AChEs *in vivo*, presence of multiple copies and alleles of AChE genes aides *R. microplus* survival against selection pressure. Therefore, frequency distribution studies of the SNPs associated with OP resistance needs to be conducted in tick populations of various geographic areas to allow forecasting the effective life of OPs.

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