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Review Article

Putative target sites in synganglion for novel ixodid tick control strategies

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ABSTRACT

Acaricide resistance is a global problem that has impacts worldwide. Tick populations with broad resistance to all commercially available acaricides have been reported. Since resistance selection in ticks and their role in pathogen transmission to animals and humans result in important economic and public health burden, it is essential to develop new strategies for their control (i.e., novel chemical compounds, vaccines, biological control). The synganglion is the tick central nervous system and it is responsible for synthesizing and releasing signaling molecules with different physiological functions. Synganglion proteins are the targets of the majority of available acaricides. In this review we provide an overview of the mode-of-action and resistance mechanisms against neurotoxic acaricides in ticks, as well as putative target sites in synganglion, as a supporting tool to identify new target proteins and to develop new strategies for tick control.

1. Introduction

Ticks are arthropods that parasitize several animal classes and present blood feeding behavior in most developmental stages (Mans, 2014; Dantas-Torres et al., 2019). These parasites are distributed worldwide and are the vectors of pathogens to animals and humans. An infected tick feeding on a non-infected host can lead to the transmission of pathogens that are harmful to the host health (United States Department of Health and Human Services, 2020; Dantas-Torres et al, 2012; Perveen, et al., 2021; TBDWG, 2018). Tick-borne diseases include mainly anaplasmosis, babesiosis, and theileriosis in animals, and spotted fever, ehrlichiosis, anaplasmosis, Powassan virus disease and Lyme disease/ borreliosis in humans (Perveen, et al., 2021; Sonenshine and Roe, 2014; Lew-Tabor and Rodriguez Valle, 2016).

Ixodidae is a family of hard ticks occurring in temperate, subtropical, and tropical regions (Apanaskevich and Oliver, 2014). *Ixodes, Haemaphysalis, Hyalomma, Amblyomma* and *Rhipicephalus* are the Ixodidae genera of most importance worldwide regarding transmission of pathogens that cause human or veterinary diseases (Boulanger et al., 2019; TBDWG, 2018).

Ixodes ricinus, Ixodes scapularis, Ixodes persulcatus and *Ixodes pacificus* are the main vectors of *Borrelia burgdorferi* genospecies, the agents of Lyme disease/borreliosis, which is critical to human health being the most common tick-borne disease, especially in the US (United States Department of Health and Human Services, 2020; Mead, 2015; Steere et al., 2004; TBDWG, 2018). Another ixodid tick of medical importance is *Ixodes holocyclus*, endemic in Australia, which causes toxicosis inducing paralysis in humans and several animal species, including birds, dogs, cats, among others (Barker and Walker, 2014; Hall-Mendelin et al., 2011; Raghavan et al., 2021).

Haemaphysalis longicornis is native from Eastern Asia and invasive in Australia, New Zealand, and recently in the United States, in part due to its ability to parasitize different hosts (United States Department of Health and Human Services, 2020; TBDWG, 2018). This tick species is the main vector of *Theileria* protozoa in Asia (Heath, 2016; Irvin, 1987; Tufts et al., 2019). *Theileria sergenti* is transmitted to domestic livestock and can lead to death, being responsible for major economic losses in Asian countries (Liu, et al., 2010; Song and Sang, 2003; Tanaka et al.,

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1993). Also in Asia, mainly in China, *Hyalomma asiaticum* ticks are important vector of pathogens, among them Crimean–Congo hemorrhagic fever virus and the agent of Q-fever, *Coxiella burnetii* (Apanaskevich and Horak, 2010; Chen et al., 2010; Duron et al., 2015; Jia et al., 2022; Wu et al., 2013).

The lone star tick, *Amblyomma americanum*, can parasitize a variety of animals, being one of the most aggressive vector of pathogens and an important tick species that affects public health and the economy in the United States (United States Department of Health and Human Services, 2020; Goddard and Varela-Stokes, 2009; Levin et al., 2017; TBDWG, 2018). All motile stages can feed on humans and spread *Rickettsia rickettsii* (Maver, 1911). Recently, several studies have also associated red meat allergy to galactose-α-1,3-galactose (alpha-gal sugar) inoculated during *A. americanum* tick bite (Commins et al., 2011; Commins and Platts-Mills, 2013; Crispell et al., 2019; Macdougall et al.,2022; Mitchell et al., 2020; Sharma et al., 2021; van Nunen, 2015; TBDWG, 2018). In the Caribbean, Central and South America, other species of the genus *Amblyomma* play roles in the transmission of pathogenic *Ehrlichia* sp. (*Amblyomma variegatum*) and *Rickettsia* spp. (*Amblyomma cajennense* sensu lato., *Amblyomma mixtum, Amblyomma sculptum*, and *Amblyomma ovale*) (Camus and Barre, 1995; Estrada-Peña et al, 2019; Nava et al., 2014).

The brown dog tick, *Rhipicephalus sanguineus* s.l., is widely distributed in the world and parasitize humans and animals. This tick species complex is responsible for transmitting multiple pathogens, such as *Babesia* protozoa, and also the bacteria *Ehrlichia* and *Rickettsia* (Dantas-Torres, 2008; Dantas-Torres et al., 2006; Estrada-Peña and Jongejan, 1999; Jongejan and Uilenberg, 2004). The cattle tick species, *Rhipicephalus microplus, Rhipicephalus annulatus* and *Rhipicephalus australis*, are of great economic importance in the world, given its widespread distribution across cattle-producing areas in the tropics and subtropics, and the transmission of *Babesia bovis, Babesia bigemina* and *Anaplasma marginale* (Ali et al., 2016). Cattle tick parasitism leads to host anemia and consequently decrease in meat and milk production, representing one of the main causes of losses in livestock industry (Jongejan and Uilenberg, 2004; Jonsson, 2006; Perveen, et al., 2021). Annual economic losses caused by *R. microplus* infestation reach US$ 3.2 billion in Brazil alone (Grisi et al., 2014).

These different tick species are responsible for the major ixodid tick-borne diseases reported worldwide and their increased abundance and range expansion could be related to many factors, including climatic, ecological and anthropological changes (Medlock et al., 2013). Currently, it is known that the interaction of humans, domestic and wild animals,and vectors is essential to pathogen transmission (Sprong et al., 2018).

Treatment of animal hosts with synthetic chemical pesticides (acaricides) has been the major approach to reduce tick infestations and prevent the transmission of tick-borne pathogens. There are seven chemical classes marketed worldwide for tick control in domestic animals, namely: organophosphates, synthetic pyrethroids, macrocyclic lactones, formamidines, benzoylphenyl ureas, phenylpyrazoles and isoxazolines (Gassel et al., 2014; Reck et al., 2014; Rufener et al., 2017). However, the use of these chemical compounds over the years led to the selection of tick populations resistant to most of these drugs (Jongejan and Uilenberg, 2004). Interestingly, *R. microplus* is the tick species with the highest number of reports of resistance worldwide, having developed resistance to all major acaricide classes marketed for its control (Dzemo et al., 2022; Rodriguez-Vivas et al., 2018; Vilela et al., 2020). Also, field populations with broad resistance to acaricides have been described in Brazil (Klafke et al., 2017; Reck et al., 2014).

Currently, a central concern regarding tick control methods is identifying strategies that are both effective and environmentally friendly (de la Fuente et al., 2007). In this context, biological control (biocontrol) methods have been explored (Samish et al., 2004). The introduction of a competitive species in the same habitat of pest species is a classical control method. However, this tool has disadvantages when both species are non-native to the affected area, or if the predator attacks non-target species (Ostfeld et al., 2006; Stiling, 2004). Therefore, it is important to perform pre-release risk assessment (Reinbacher et al., 2021; Simberloff, 2012). Entomopathogenic fungi, like *Metarhizium brunneum* (formerly *Metarhizium anisopliae*), have proven an effective alternative to reduce *I. scapularis* population, while also indicating to be a safe approach, since it does not affect non-target arthropods communities that may be present at the application site. On the other hand, more than one application is needed to obtain positive results (Bharadwaj and Stafford, 2010; Fischhoff et al., 2017). Application of *M. brunneum* in association with acaricides has been shown to increase effectiveness of the treatment in the control of resistant *R. microplus* strains (Webster et al., 2015), suggesting biocontrol methods in combination with other strategies as an alternative to control tick infestations (Beys-da-Silva et al., 2020).

A sustainable, eco-friendly and economically favorable approach to tick control is the use of vaccines (de la Fuente et al., 2007, 2017; Guerrero et al., 2012b). Therefore, many efforts have been made to develop an efficient vaccine that confer protection against different tick populations (Guerrero et al., 2012b; Parizi et al., 2012). Based on recombinant Bm86 (midgut glycoprotein antigen), two vaccines were developed against *R. microplus* from Australia and Cuba (TickGARD and GAVAC, respectively) (Canales et al., 1997; Willadsen et al., 1995). TickGARD vaccine is not currently available for use, while GAVAC it is still commercialized. However, both vaccines failed to show efficiency worldwide (Guerrero et al., 2012b). On the other hand, different studies have shown that Bm86 and its homologues induce protection against *R. annulatus* (Fragoso et al., 1998), *R. australis* (Hüe et al., 2017) and *Rhipicephalus decoloratus* (Odongo et al., 2007), which can be very useful due to eventual coexistence of *R. microplus* and other tick species across the same area (Parizi et al., 2012). Nevertheless, to date, no effective vaccine against *R. microplus* and other ticks has been brought forward. Thus, the control of tick parasitism and tick-borne diseases in humans and animals is still dependent on acaricide treatment. Serious limitations associated with the application of acaricides have intensified the search for novel tick control methods (Rodriguez-Vivas et al., 2018).

2. Resistance mechanisms to acaricides

Acaricide resistance is defined as a decrease in the susceptibility of a parasite population to a drug, which is a global concern (Devaney, 2013). It was demonstrated that 79% of *R. microplus* from Rio Grande do Sul state (Brazil) present multiple resistance to three or more acaricides tested (cypermethrin, amitraz, chlorpyriphos, ivermectin, and fipronil) (Klafke et al., 2017). Three major mechanisms of resistance to acaricides/insecticides are known: cuticle thickening (reducing chemical penetration) (Schnitzerling et al., 1983), target-site insensitivity (Castro Janer et al., 2019), and detoxification metabolism (Le Gall et al., 2018), with most studies focusing on the last two.

2.1. Target-site insensitivity

In arthropods, similar to other animals, voltage- and ligand-binding gated ion channels are important components of the nervous system, enabling the propagation and processing of cell signaling (Smarandache-Wellmann, 2016). A common resistance mechanism involves a point mutation causing amino acid sequence modifications in ion channels, which could confer target-site resistance to acaricides (Guerrero et al., 2012a).

Neurotoxic pesticides commonly used for tick control, like synthetic pyrethroids, act on arthropod voltage-sensitive sodium channels (Na^+ channels) (Fig. 1) (Kumar et al., 2020). Voltage-gated ion channels play essential roles in the nervous system, since they are involved in detection and transmission of intracellular chemical signals (Smarandache-Wellmann, 2016). Interestingly, the central nervous system of ticks, named synganglion, is the main target of several acaricides (Lees

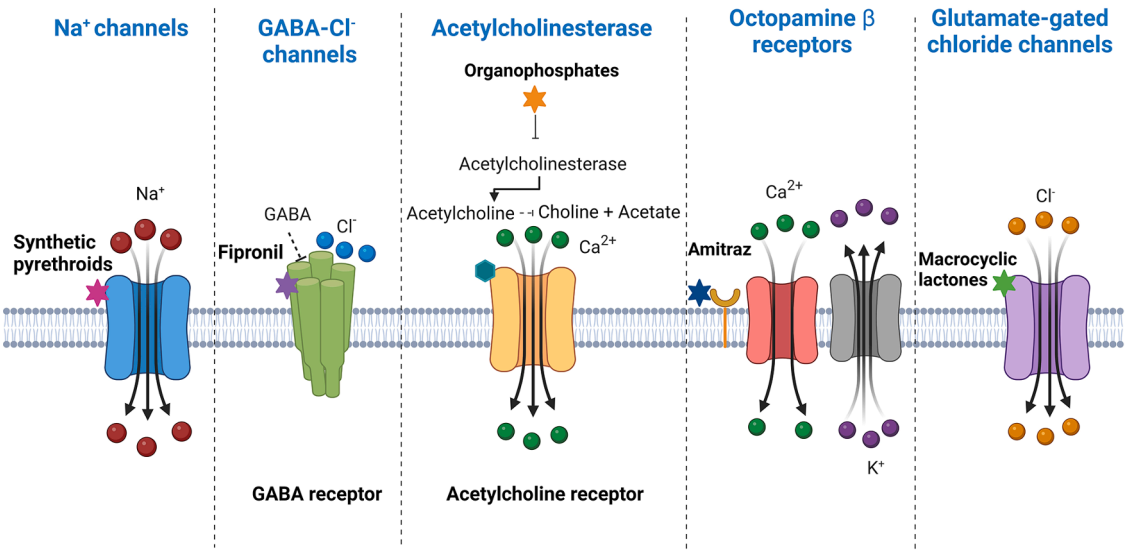

Fig. 1. Targets of commercial acaricides. The main commercial acaricides have neurotoxic activity, interfering in the functions of different channels or receptors in the cells of the central nervous system.

et al., 2010). However, the insensitivity of these channels to drugs has been described in various arthropod species (Du et al., 2016). Specifically, mutations in the ion channels are the one of the factors in the mechanism of acaricide resistance (Klafke et al., 2020; Kumar et al., 2020) and was first described in DTT-resistant house flies (Busvine, 1951). The role of chemical compounds on Na^+ channels is variable, but mainly relate to the extension of activation and inactivation steps (Hemingway et al., 2004; Lund and Narahashi, 1983; Vais et al., 2001).

The most popular acaricides, the synthetic pyrethroids, act on voltage sensitive sodium channels (Na^+ channels) (Kumar et al., 2020). These channels are composed by four homologous domains (DI, DII, DIII and DIV) and six transmembrane helices (S1–S6), while S1 to S4 constitute the voltage-sensing domain, the loop connecting S5 and S6 form a pore and, in response to membrane depolarization, the opening of the channels occurs (Auteri et al., 2018; Catterall, 1995; Oliveira et al., 2013). Mutations in the amino acid sequence of Na^+ channels, known as knockdown resistance (kdr) or super kdr mutations, has also been reported (Du et al., 2016; Kushwah et al., 2020). Kdr mutations in the amino acid sequence from DII has been already related to the increase of pyrethroid resistance in *Aedes aegypti* (Saavedra-Rodriguez et al., 2007; Srisawat et al., 2010). Substitutions from leucine (Leu) to phenylalanine (Phe) in DII of the channel, associated with resistance, were also detected in *Anopheles gambiae* (Martinez et al., 1998). This domain is highly conserved among *Rhipicephalus* spp. ticks (Vudriko et al., 2018) and kdr mutations leading to change in amino acid sequence from Leu to isoleucine (Ile), in DIIS4-5 from Na+ channels, were already identified in *R. microplus* resistant to cypermethrin (Morgan et al., 2009; Vudriko et al., 2018). Also, similar mutations were detected in this tick species from India (Nagar et al., 2018) and in *Rhipicephalus appendiculatus* from Uganda (Vudriko et al., 2018), while super-kdr substitutions were described in *R. decoloratus* (Vudriko et al., 2017). Furthermore, other studies analyzed *R. microplus* pyrethroid-resistant strains from Mexico and United States and identified target-site insensitivity due to the occurrence of kdr and super-kdr mutations in DII and DIII of Na^+ channels amino acid sequence (He et al., 1999; Stone et al., 2014), as well as a point mutation in DIIIS6 nucleotide sequence, causing the substitution from Phe to Leu in amino acid sequence, were also identified in *R. sanguineus* s.l. resistant to pyrethroids phenotype (Klafke et al., 2017).

Gamma-aminobutyric acid-gated chloride channel (GABA-Cl) was also described as a target site for several insecticides (i.e. cyclodienes, lindane and fipronil) which act as antagonists, blocking GABA and causing hyperexcitation of the central nervous system (CNS) (Fig. 1) (Bloomquist, 2003, 2001, 1994; Matsumura and Ghiasuddin, 1983). Besides its activity on GABA-Cl, fipronil (as well as fipronil sulfone, a major metabolite obtained from fipronil oxidation metabolism) has a role in inhibiting glutamate-gated chloride channels (Glu-Cl) in cockroaches (Bobé et al., 1998; Hainzl et al., 1998; Zhao et al., 2005, 2004). In *R. australis*, one amino acid substitution from Thr to Leu on the position 290 of GABA-Cl was associated with resistance to dieldrin (Hope et al., 2010). In fipronil- and lindane-resistant *R. microplus* from Brazil and Uruguay two different substitutions were found on GABA-Cl, A286S and A286L (Castro Janer et al., 2019).

Another target site known to be involved in pesticide resistance is acetylcholinesterase, that degrades acetylcholine (Ach) promoting the neurotransmitter reuptake disrupting the neurotransmission (Colović et al., 2013). However, when organophosphate acaricides bind to this enzyme they inhibit the acetylcholinesterase activity and consequently the hydrolyses of acetylcholine leading to the accumulation of this neurotransmitter in insect CNS (Fig. 1) (Casida, 1956; Casida and Durkin, 2013; Nostrandt et al., 1997).

A partial transcript of acetylcholinestarase-encoded gene (*AchE*) was described in synganglion from *R. sanguineus* s.l. (Lees et al., 2010), while three *AchE* were identified in *R. microplus* (viz. BmAchE1, BmAchE2 and BmAchE3). Interestingly, there was a low similarity among these sequences, also no point mutations were detected in nucleotide sequence from susceptible and resistant isolates to organophosphates, suggesting that other locus or mechanism could be involved (Baxter and Barker, 1998; Hernandez et al., 1999; Temeyer et al., 2004). However, in latest published studies, single nucleotide polymorphisms (SNPs) have already been described at least in two (*AchE1* and *AchE3*) of the three *AchE* from *R. microplus* and associated to organophosphates resistance (Bendele et al., 2015, Temeyer et al., 2010). A substitution from glutamine (Glu) to arginine (Arg) in the BmAchE3 sequence conferred target insensitivity to organophosphates (Temeyer et al., 2007), in addition was found high frequency of this mutation in *R. microplus* resistant strains (Temeyer et al., 2009), besides that it was also present in wild type ticks, thus different mechanisms could act synergistically to provide tick resistance. Indeed, in insects was proposed that several mutations could be occurring at the same time in *AchE* sequences, promoting an increase in the resistance ratio (Mutero et al., 1994). Accordingly, the occurrence of five mutations identified in *D. melanogaster* AchE were related to increase of the organophosphate's insensitivity. In combination, these substitutions presented stronger resistance potential to this pesticide class than when

tested alone, with exception of Gly to Val mutation (G262V position) which led to high resistance ratio (Walsh et al., 2001).

Currently, three arthropod octopamine receptors (AOR) classes have been described: α-adrenergic-like octopamine receptors (αAOR), octopamine/tyramine receptors (OCT/TYR) and β-adrenergic-like octopamine receptors (βAOR) (Corley et al., 2012; Evans and Maqueira, 2005; Han et al., 1998; Nagaya et al., 2002). Formamidines (like amitraz) act as agonists, stimulating AOR and causing CNS toxicity and death (Fig. 1) (Evans and Gee, 1980; Nathanson, 1985). This pesticide is also suggested to have a role in tyramine receptors activation (Gross et al., 2015). Mutations on OCT/TYR, threonine to proline (T8P) and leucine to serine (L22S), have been associated with *R. microplus* resistance to amitraz in Brazil, Philippines, India, Zimbabwe, and South Africa (de La Canal et al., 2021; Alota et al., 2021; Jyoti et al., 2021; Sungirai et al., 2018; Robbertse et al., 2016). However, mutations on βAOR (viz. threonine to proline - T60P; isoleucine to phenylalanine - I61F; isoleucine to threonine - I61T and tyrosine to serine - Y88S) with amitraz resistance in ticks (Jonsson et al., 2018, Takata et al., 2020). Hence, it can be suggested that amitraz resistance in cattle ticks may result from mutations in different octopamine receptors.

2.2. Detoxifying proteins and detoxification pathways

Drug detoxification mechanisms are often associated with enzymes such as esterases, cytochrome P450 (CYP450), and glutathione S-transferases (GSTs) (Koirala et al, 2022; Le Gall et al., 2018), which participate in different phases of pesticide metabolism. To minimize the deleterious effects caused by pesticides, enzymes from phase I (e.g. esterases and CYP450) perform the reduction, oxidation and/or hydrolysis of chemical compounds, with the formed products acting as substrates in the next step. In phase II (conjugation), enzymes such as GSTs render these compounds less toxic and more hydrophilic, facilitating the transport out of the cell (Perry et al., 2011). Moreover, an additional phase, named 0 or III, may also be associated with these processes, controlling the flux of molecules which have not yet reached intracellular compartments, or promoting the excretion of already detoxified drugs by ATP-binding cassette transporters (ABC transporters) (Ishikawa, 1992; Lara et al., 2015; Le Gall et al., 2018; Pohl et al., 2012; Szakács et al., 2008).

Many pesticides, such as organophosphates and synthetic pyrethroids, are esters which possess cyclopropacarboxylic, carbamic and phosphoric acids substituted, thus being subject to degradation by esterases (Devonshire, 1991). However, there are other ways by which these enzymes could promote drug resistance. Mutations in carboxylesterases genes associated with pyrethroid resistance have been described in arthropods (Hemingway and Karunaratne, 1998; Hernandez et al., 2000). Carboxylesterases have a role in pesticide detoxification, and besides sequence mutations, overexpression of these enzymes has also been reported in pyrethroid resistant arthropods, like *Musca domestica* (Feng et al., 2018). In coumaphos-resistant *R. microplus* ticks, an increased hydrolysis capacity of carboxylesterase was detected which is possibly associated to organophosphate resistance (Villarino et al., 2003)

Cytochrome P450 is another superfamily of enzymes involved in endogenous processes, xenobiotics activation and detoxification metabolism, being ubiquitously distributed in many organisms (Bergé et al., 1998; Guzov et al., 1996). In detoxification pathways performed by monooxygenases, two oxygen atoms are involved in the reactions: while one atom is reduced to H_2O, the other is incorporated to the substrate, preparing the substrate to enter phase II metabolism. However, in some cases, these formed products may be more toxic than the initial compounds (Hodgson, 1985). In insects, CYP450 have an important role in resistance to chemical compounds, as indicated by the overexpression of these enzymes and increased activity in resistant organisms (Liu et al., 2015).

After phase I metabolization of toxicants, GSTs play an important role in the final steps of chemical detoxification (Sheehan et al., 2001). These cytosolic enzymes act by catalyzing the conjugation to glutathione (GSH), facilitating that this more hydrophilic substrate be transported out of the cell (Sheehan et al., 2001). In ticks, the GSTmu was detected in different tissues in larvae and adults from *R. annulatus,* suggesting an important physiological role for this enzyme. In addition, a homologous protein was also identified in *Hyalomma dromedarii* and *Rhipicephalus* sp., and interestingly, this protein was not present in the argasidae tick *Ornithodoros moubata* (Shahein et al., 2008).

Lastly, ABC transporters are a broad protein family present in several organisms (Higgins, 2001) and their importance in promoting excretion of endo- and xenobiotics has been reported (Buss and Callaghan, 2008; Lara et al., 2015). These proteins act as active transporters and possess drug-binding sites and two ATP-binding, providing energy for substrate transport. Thereby, once ATP binding and hydrolysis occurs, the cassette is able to transport the hydrophilic substrate to the extracellular space, across the cell membrane (Dermauw and Van Leeuwen, 2014; Nobili et al., 2006). Also, P-glycoproteins (P-gp or MDR1 of the ABCB family), which are related to drug uptake and excretion, have been reported as a protection mechanism against pesticide in mosquitoes, including a multidrug resistance pathway, and may be the first line of defense of cells (Bain and LeBlanc, 1996; Buss et al., 2002; Danø, 1973; Germann and Chambers, 1998; Juliano and Ling, 1976).

3. Tick synganglion

Located in the anterior portion of the tick's body, the synganglion is a fused nerve mass that appears as a single structure representing the entire CNS of these parasites (Šimo et al., 2013). This organ is a major site for neural integration of physiological processes essential to tick survival, reproduction and development, since synganglion neuropeptides control many different bodily processes throughout each life stage of the tick (Rispe et al., 2022) In adult ticks, this organ is approximately 424 μm and 338 μm long in females and males, respectively, with similar basic arrangement: no segmentation, positioned around the esophagous, being subdivided in supraesophageal and subesophageal ganglia. In addition, it has a perigangliomic sheath that supplies this organ with fresh hemolymph, and projections from Haller's organ that originate in the olfactory lobes of the synganglion (Lees and Bowman, 2007; Menezes et al., 2021; Prullage et al., 1992). In *R. sanguineus* s.l., no differences were observed in synganglion morphology among the different life stages, confirming that this tissue remains unchanged from larvae to adults (Roma et al., 2014, 2012). However, 72 h after detachment from the host, *R. microplus* females present a higher level of DNA fragmentation in the synganglion, resulting from apoptosis (Freitas et al., 2007).

Synganglion influences tick physiological regulation, performing several functions as a neurosecretory system that synthesizes and releases signaling molecules which target different organs, like hormones and neuropeptides (Šimo and Park, 2014; Lees and Bowman, 2007; Šimo et al., 2013; Wulff et al.,2022) (Fig. 2). Gene ontology analysis in *Dermacentor variabilis* and *R. sanguineus* s.l. showed that the main functional categories transcribed in the synganglion from unfed, partially fed and fully fed females were cellular process, metabolic process and biological regulation, respectively. In addition, transcripts were differentially regulated according to the feeding stage, including most neuropeptides which were downregulated with the onset of blood feeding (Bissinger et al., 2011; Lees et al., 2010). Neurosecretory cells were detected by immunocytochemistry in *Ornithodoros parkeri* synganglion, confirming this organ as a neurohemal site in ticks (Zhu and Oliver, 1991). Also, in *R. microplus*, a transcriptome of synganglion showed that the most abundant transcripts are related to secretion, energetic metabolism and unknown categories, and that neuropeptides precursors represented around 6% of transcripts (Waldman et al., 2022). Neuropeptides produced by synganglion could act as neurohormones, neurotransmitters or neuromodulators, influencing social behavior,

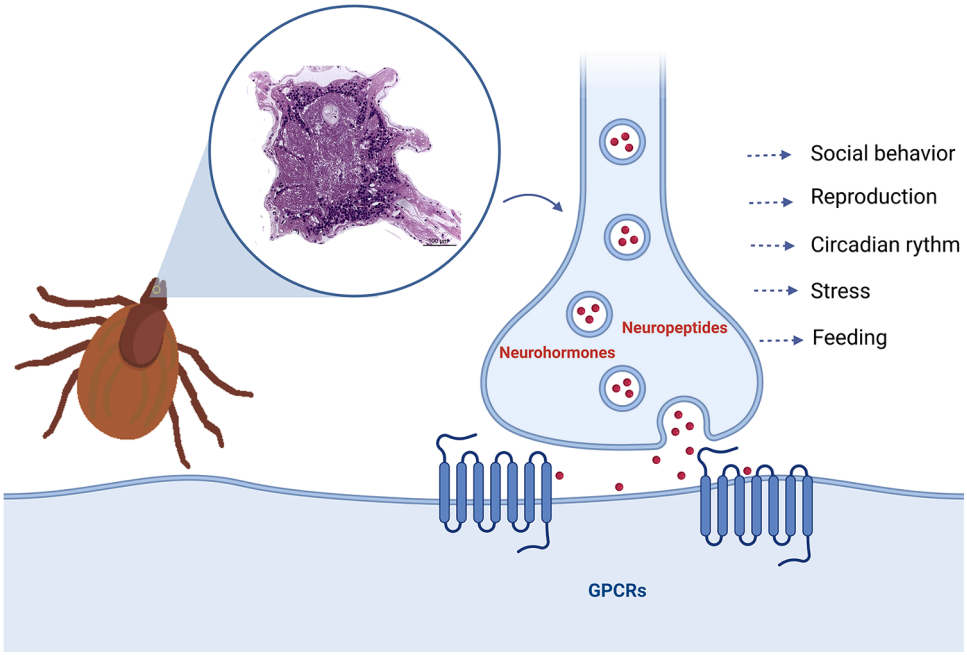

Fig. 2. Schematic view of tick synganglion functions. The neuropeptides and/or neurohormones produced and released by the synganglion bind mainly to G protein-coupled receptors (GPCRs) and have several biological activities that control tick physiology.

learning, circadian rhythm, stress, feeding, reproduction and memory of insects (Burbach, 2011; Schoofs et al., 2017). In the desert locust, *Schistocerca gregaria*, the most comprehensive neuropeptidome assay performed identified 81 neuropeptide precursors using genomic and transcriptomic approach, many of these peptides are mostly expressed in the CNS (Ragionieri et al., 2022). In *A. aegypti*, several neuropeptides were detected in CNS, but also in midgut, showing that these peptides are not restricted to the CNS and are involved in endocrine system of mosquitoes (Predel et al., 2010). In addition, another study has shown that neuropeptides from decapods are similar to those of insects, and although these peptides may not have same role, the sequence conservation facilitates research on neuropeptidomes in different arthropods (Veenstra, 2016). Despite extensive knowledge in insects, little is known about these peptides in ticks. Immunohistochemical staining showed the presence of a complex neuropeptidergic network of molecules produced by endocrine cells and central and peripheral neurons in the *R. appendiculatus* synganglion (Šimo et al., 2009). In *I. scapularis*, 20 neuropeptides were detected by mass spectrometry approach, and this neuropeptidomic study has shown that most of these peptides were similar to *A. americanum* neuropeptides (Neupert et al., 2009). Interestingly, in synganglion transcriptome from *I. scapularis,* 15 putative neuropeptide precursors and 14 receptors were identified, furthermore, transcripts for convertases, that convert precursors into mature sequences, were also detected (Egekwu et al., 2014). Also, the transcription of 14 neuropeptides and five receptors were identified in *D. variabilis* (Donohue et al., 2010), and further research has shown that neuropeptides, as well as their receptors, can be differentially expressed depending on the tick`s developmental stage (unfed, partially or fully fed females) (Bissinger et al., 2011). Currently, an updated list of neuropeptides has identified 52 precursors in *R. microplus* transcriptome and in the genome of hard ticks, such as *R. microplus, R. sanguineus* s.l., *I. scapularis, I. persulcatus, Dermacentor silvarum, H. longicornis, H. asiaticum* (Gulia-Nuss et al., 2016; Jia et al., 2020), showing that these peptides are conserved in different tick species (Waldman et al., 2022). In comparison, only 38 genes and 37 neuropeptide transcripts were identified in the genome and transcriptome from *I. scapularis* cell line, respectively. Interestingly, the level of neuropeptide transcription was influenced by *Anaplasma phagocytophilum* infection, which suggests a neuronal component in tick-pathogen interaction (Mateos-Hernández et al., 2021).

Most acaricides modulate and target synganglion, and although peptide receptors have been identified in different tick species, it is interesting to note that currently none of the neuropeptide receptors are target for acaricides (Roma et al., 2014; Xiong et al., 2020). G-protein coupled receptors (GPCRs) have been linked to effects on several pathways of arthropod physiology, such as development, reproduction, metabolism and ecdysis (Ngai and McDowell, 2017). In *A. aegypti* genome, 135 GPCRs were identified, and a conservation among sequences from this insect and *A. gambiae* and *Drosophila melanogaster* was suggested (Nene et al., 2007). In ticks, the first dataset of *R. microplus* GPCRs identified 112 candidates distributed into the rhodopsin, secretin and glutamate families (Guerrero et al., 2016). In a bioinformatic analysis, novel GPCRs were predicted in the transcriptome of Haller's organ from *R. australis* (Munoz et al., 2017). Moreover, *R. microplus* kinin sequences were reported and had activity on a kinin receptor (an invertebrate-specific GPCR) (Pietrantonio et al., 2018; Xiong et al., 2020). Additionally, the expression of this receptor was detected in *R. microplus* midgut, and a role in reproduction was shown (Brock et al., 2019). In *R. sanguineus* s.l., kinin receptor transcription was identified in the synganglion, salivary glands, gut, Malpighian tubules and oviduct tissues, with more transcripts being present in salivary glands and midgut (Lees et al., 2010). Taken together, these data facilitate the search for new targets for pesticide development.

Neuroendocrine regulation was also shown to act on the oogenesis of *O. parkeri*, since vitellogenesis was inhibited when ovary was separated from the synganglion in tick body, but when synganglion was transplanted again, from unfed or fed females, the complete maturation of the oocytes I (Oliver et al., 1992). Similarly, in *O. moubata* it was demonstrated that the transplantation of synganglion from fed mated females to virgin females induced vitellogenesis, but there was no effect on oviposition, suggesting that this organ has pleotropic functions and also produces stimulating factors for oogenesis (Connat et al., 1986). Thus, the knowledge and understanding of tick physiology and neurobiology, as well as the detection of potential new targets and molecules with acaricidal activity, such as peptides and interacting molecules, can help in the development of alternative methodologies for the tick control,

overcoming the problem of acaricide resistance (Bendena, 2010; Caers et al., 2012; Guerrero et al., 2012b; Saramago et al., 2018).

4. Identification of active molecules and potential targets for tick control

Acaricide application is the most common method for controlling tick infestation, however the continuous use of these compounds increases the selective pressure, favoring the emergence of resistant tick populations. Since the use of acaricides causes an inexorable selection for acaricide-resistant tick populations, there is a continuous need to develop and introduce new commercial products to control ticks. Thereby, there are different strategies to discover new putative active ingredients, mostly focusing on the identification of natural product-based molecules and selection of compounds from complex synthetic chemical libraries. Both approaches have several advantages and disadvantages (Adenubi et al., 2018; Chen et al., 2019; Nyahangare et al., 2015; Stratton et al., 2015). Moreover, the search for novel molecules as potential targets for acaricides is needed, and a better understanding of tick physiology is instrumental to achieving this end, which might lead to the identification of new compounds with potential ectoparasiticide activity (Rufener et al., 2017; Saramago et al., 2018).

Considering that the synganglion represents an important organ in the control of tick physiological processes (as summarized in Fig. 2), metabolic alterations caused by neurotoxic agents could lead to important effects, including functional dysregulation leading to death (Pereira et al., 2017; Roma et al., 2014). A new class of pesticides, named isoxazolines, acts as a non-competitive antagonist of GABA-Cl channels, specifically on arthropod RDL (resistance to dieldrin gene) as main target, and less extensively on Glu-Cl. In addition, this parasiticide presents a stronger inhibition of GABA-Cl than picrotoxinin and dieldrin, and has superior inhibitory and insecticide/acaricide activity than fipronil in the RDL target (Gassel et al., 2014). Similar results were observed in ticks, flies, and sea lice, and no cross-resistance among dieldrin, fipronil and isoxazoline was observed in these arthropods, showing that this pesticide has different binding sites compared to these other known GABA-Cl blockers (Rufener et al., 2017). Also, fluralaner, a molecule from the isoxazoline class, showed potent acaricidal activity against all life stages of *R. sanguineus* s.l. and *O. moubata* nymphs, when used by contact or feeding exposure pathways, respectively (Williams et al., 2015). Okaramine, an alkaloid Glu-Cl activator, was obtained from *Penicillium simplicissimum* and showed a toxic effect against *Bombyx mori* silkworm larvae, but not against human GABA-Cl and glycine-gated chloride, highlighting its use as a putative insecticide (Furutani et al., 2015; Hayashi et al., 1989). Interestingly, this molecule acts on binding sites that are different than those of ivermectin, suggesting that the resistance mutations that affect ivermectin activity could be ineffective against okaramine action (Furutani et al., 2017). In addition to their role in insects, an acaricide activity was also tested for okaramine against *I. scapularis*, showing that, unlike other Glu-Cl blockers such as picrotoxin and fipronil, okaramine activated this channel in a dose-dependent manner. An inhibition of the ivermectin response on Glu-Cl channel by the fungal alkaloid was also observed, confirming that both molecules act on different target sites (Furutani et al., 2018).

Tyramine and octopamine are present in the CNS and act as neurotransmitters that regulate a variety of behavior and physiological processes in arthropods, allowing them to respond to the environment according to external stimuli received. The use of agonists and antagonists of octopamine and tyramine receptors, respectively, results in CNS excitation, leading to similar physiological effects (Hunt, 2007; Roeder et al., 2003). In tick females, octopamine injection was shown to block oviposition, although other β-adrenergic agonists, such as synephrine and apormophine, showed different effects and no inhibitory action on oviposition (Booth, 1989). On the other hand, it was shown that an alteration in tyraminergic pathway (α-adrenergic) inhibited oviposition in *R. microplus* more potently than octopamine. These results indicated that the susceptible strains used could be resistant to amitraz, which acts as an octopamine agonist, and therefore were more tolerant to this neurotransmitter action and did not show the same effect on oviposition (Cossío-Bayúgar et al., 2012).

As other examples of CNS molecules in pest management, neuropeptides have been suggested and investigated. However, due to instability, they could not be applied alone, requiring compound combinations to prevent degradation by peptidases and protect these peptides until reaching their target sites (Nachman et al., 2002). Insect kinins are important peptides that present a variety of functions, including in the excretory system of insects (Coast, 2007). Due to the presence of sites susceptible to peptidase action, the use of kinin analogs, which are more stable and therefore resistant to degradation, has been studied (Nachman et al., 2002). Thus, biostable molecules, such as α-aminoisobutyric kinin analog or polyethylene glycol polymer-conjugated kinin, have been shown to act on mosquito and tick receptors, as well as unconjugated peptides, and may be a useful tool to study the role of kinin in arthropods physiology and subsequent application in tick control.

Due to the difficulty in identifying new acaricides with neurotoxic potential that could serve for ectoparasite control, molecules with different physiological targets have been tested. Triosephosphate isomerase (TIM) is an enzyme that participates in glycolysis and gluconeogenesis metabolism, catalyzing the interconversion of glyceraldehyde 3-phosphate and dihydroxyacetone phosphate (Knowles, 1991). Structural changes in *Plasmodium falciparum* TIM, due to modification in a cysteine residue, led to the loss of enzymatic activity (Maithal et al., 2002). In ticks, TIM inhibitors were evaluated for their acaricidal efficacy, revealing that, out of the 227 compounds tested, four were able to inhibit enzymatic activity, with a decrease in the percentage of viable cells and reduction in *R. microplus* larvae hatching rate also reported (Saramago et al., 2018). Inhibitors that prevent the degradation of tyrosine, an amino acid obtained from the blood meal, may be a good and safe alternative for parasite control (Sterkel et al., 2016). Other studies have showed that the exposition to anonaine, an alkaloid isolated of plant *Annona crassiflora* (Bezerra et al., 2022) or synthetic molecules (Ozelame et al., 2022) reduce the activity of glutathione-S-transferase and increase tick mortality, suggesting GST as potential target for development of new acaricides mitigating resistance to acaricides (Obaid et al., 2022; Umetsu and Shirai, 2020).Besides inhibitors, natural compounds have also been tested for their pesticidal activity, and present great interest for parasite control, mainly for having reduced environmental impact compared with chemical acaricides (Adenubi et al., 2018). In this context, essential oils extracted from oregano (*Lippia graveolens*), rosemary (*Rosmarinus officinalis*), and garlic (*Allium sativum*) showed high toxicity in a *R. microplus* larval packet test, reaching 100% of mortality at the highest concentrations evaluated (Martinez-Velazquez et al., 2011). Moreover, mortality and reduced oviposition were also observed in engorged ticks exposed to oregano compounds, and these effects may be due to the presence of thymol, carvacrol and p-cymene, which represent the main components of this plant species (Flores-Fernández et al., 2016). Interestingly, sublethal concentrations of acetylcarvacrol affected oocyte development in *R. microplus* engorged females. Despite all of the stages of oocyte development (I, II, III, IV and V) being present, defects in their morphology were detected (Konig et al., 2019). Similar results were also observed in partially engorged females from *R. sanguineus* s.l., where oocyte development was impaired and only stages I and II were present in ticks that were exposed to carvacrol (Lima de Souza et al., 2019). Also, it was observed that *R. microplus* exposed to carvacrol and thymol showed an increase in the activities of glutathione-S-transferase, catalase, superoxide dismutase and glutathione peroxidase, suggesting that the generation of reactive oxygen species is the mechanisms of toxicity of these potential natural acaricides (Tavares et al., 2022). Besides carvacrol, guaiol and bunesol compounds and essential oil from *Bulnesia sarmientoi* also showed larvicidal activity against *R. microplus,*

Rhipicephalus evertsi, Rhipicephalus pulchellus, R. appendiculatus. Interestingly, tolerance to these components was observed in acaricide-resistant *R. microplus* populations when compared with susceptible ticks (Luns et al., 2021). At the same time, phyto-formulations that combine extracts from different plants species, like cumin (*Cuminum cyminum*), cinnamon (*Cinnamomum zeylanicum*) and allspice (*Pimenta dioica*) also showed potent acaricidal activity (Lazcano Díaz et al., 2019), supporting that the application of plant extracts and essential oils or their components could be an addition to the available anti-tick arsenal for the control of ectoparasites, with importantly less residual effect than chemical acaricides (Lara et al., 2015).

An interesting alternative to tick chemical control could be the use of RNA interference (RNAi) or genome editing using CRISPR/Cas9 system to silence genes related to essential physiological functions, including synganglion metabolism. In the last years, these methodologies have emerged as important biological tools for research but, several preliminary studies have been shown the potential applications in pest control (Christiaens et al., 2020; Kaduskar et al., 2022; Lester et al., 2020; Tyagi et al., 2020; Vogel et al., 2019; Yan and Lin, 2022). Genetic engineering tools have been caused controversies, however RNAi and CRISPR methodologies are easier to use and more precise than other DNA-editing tools (Lux and Scharenberg, 2017; Watters et al., 2021). The use in the field of these methodologies has many challenges, including, a better understanding of tick gene expression, methodological security and ethical issues (Christiaens et al., 2020, Hoang et al., 2022; Tirloni et al., 2020; Willow et al., 2021), however different approach could be used reduce and eliminate these obstacles to make these techniques more suitable for pest control (Mehlhorn et al., 2021).

Several potential targets and alternative methodologies have been proposed for tick control, and an increasing knowledge about tick metabolism provides an essential basis for commercial acaricidal development. Nevertheless, the identification of these targets still needs further research and the continuous efforts to understand tick physiology will likely eventually lead to novel control strategies capable of circumventing current acaricide-resistance mechanisms.

CRediT authorship contribution statement

Jéssica Waldman: Writing – original draft, Writing – review & editing. **Guilherme Marcondes Klafke:** Writing – original draft, Writing – review & editing. **Lucas Tirloni:** Writing – original draft, Writing – review & editing. **Carlos Logullo:** Writing – original draft, Writing – review & editing. **Itabajara da Silva Vaz:** Writing – original draft, Writing – review & editing.

Declarations of Competing Interest

None.

Data availability

No data was used for the research described in the article.

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Supplementary materials

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