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REVIEW ARTICLE

Chemical Ecology of Animal and Human Pathogen Vectors in a Changing Global Climate

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Abstract Infectious diseases affecting livestock and human health that involve vector-borne pathogens are a global problem, unrestricted by borders or boundaries, which may be exacerbated by changing global climate. Thus, the availability of effective tools for control of pathogen vectors is of the utmost importance. The aim of this article is to review, selectively, current knowledge of the chemical ecology of pathogen vectors that affect livestock and human health in the developed and developing world, based on key note lectures presented in a symposium on "The Chemical Ecology of Disease Vectors" at the 25th Annual ISCE meeting in Neuchatel, Switzerland. The focus is on the deployment of semiochemicals for monitoring and control strategies, and discusses briefly future directions that such research should proceed along, bearing in mind the environmental challenges associated with climate change that we will face during the 21st century.

Keywords Livestock · Human · Pathogen vector · Semiochemical · Climate change

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Introduction

Infectious diseases affecting livestock and human health that involve vector-borne pathogens are a global problem, unrestricted by borders or boundaries, which may be exacerbated by changing global climate. The global burden of disease through the impact of pathogens and other infectious organisms, including those transmitted by vectors, can be measured using a number of parameters. For farm animals, this can be measured directly as a reduction in the amount of available food (FAO 2005). This can contribute directly to food insecurity and poverty on a global scale. For human populations, the global burden of disease can be measured in disability adjusted life years (DALYs). Approximately 40% of all DALYs lost can be attributed specifically to vector-borne diseases, along with other major diseases including acute respiratory infections, HIV/AIDS, and TB (WHO 2000). In view of these startling figures, the availability of a range of tools for control of vectors of pathogens is of the utmost importance. The aim of this article is to review, selectively, current knowledge of the chemical ecology of vectors of pathogens that affect livestock and human health in developed and developing countries, based on key note lectures presented in a symposium on "The Chemical Ecology of Disease Vectors" at the 25th Annual ISCE meeting in Neuchatel, Switzerland, with a view to the deployment of semiochemicals for monitoring and control strategies, and to discuss briefly future directions that such research should proceed along, bearing in mind the environmental challenges associated with climate change that we will face during the 21st century.

Compounds that act as broad-spectrum toxicants, i.e., insecticides, started to provide the main intervention against pathogen vectors during the latter half of the 20th century, and still do so. These include the synthetic pyrethroid

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insecticides, which were largely invented during the 1960s and 1970s by Michael Elliott and his colleagues at Rothamsted (Elliott et al. 1973). However, due to a number of factors, such as the development of insecticide resistance, their perceived negative environmental impact upon human health and the environment, and the cost of maintaining registration of insecticides for pest control, such materials may no longer be acceptable for control of pathogen vectors. In spite of this, the insect nervous system still remains a major target for insect control. The emphasis now, however, relates to non-toxic mechanisms for interfering with pest behavior and development, e.g., host and mate-seeking behavior and oviposition site selection. These are mediated predominantly by the detection of small, lipophilic molecules (semiochemicals) that are detected by specialized olfactory receptor neurons (ORNs) located either on the antennae or on the maxillary palps (Pickett et al. 2009). The potential for manipulating the behavior of vectors of pathogens in host, mate, and oviposition site selection *via* olfactory detection of semiochemicals presents opportunities for their control, *via* the development of novel repellents and attractants, provided they can be deployed through an integrated management strategy, e.g., the push-pull strategy, which has been used highly successfully for pest management in some arable crop systems(Cook et al. 2007; Hassanali et al. 2008).

Hypotheses for Developing Novel Repellents for Pathogen Vectors

The ability to manipulate pathogen vector behavior can be exploited by developing repellents based on hypotheses that relate to evolution of repellency. These fall into three classes: (1) botanicals, (2) non-host species, and (3) host-derived repellents.

Botanicals In conveying a strong plant cue, botanicals interfere with host location by haematophagous (blood-sucking) and biting flies and other arthropods. Although botanically-derived materials such as citronella oil, *Eucalyptus* spp. oils containing *p*-menthane-3,8-diol and eucamalol, and gum resins from members of the Burseraceae have been investigated for use as repellents for human or livestock protection (Nishimura and Satoh 1999; Peterson and Coats 2001; Birkett et al. 2008), the active components are highly volatile, can be readily lost, and therefore lose efficacy at a rapid rate (Lindsay et al. 1996; Chou et al. 1997). Furthermore, these agents also can cause dermatitic problems, so repeated application is not a viable option. However, iridoid nepetalactones produced by *Nepeta* spp. plants (Lamiaceae), and structurally-related compounds, have been investigated as repellents (Bernier et al. 2005; Chauhan et al. 2005; Spero et al. 2008), which may avoid some of these problems. A further concern associated with such materials is that host-seeking vectors invariably still can locate their potential host by overcoming the plant-related cues. This problem has also been observed for synthetic repellents such as *N,N*-diethyl toluamide (DEET) or Bayrepel®. For DEET, the precise mode of action has been the subject of intense debate and study since its development as a synthetic repellent from structure-activity relationship studies conducted during the 1950s. Early reports suggested that DEET modulated the electrophysiological response of lactic acid ORNs in the antennae of the yellow fever mosquito, *Aedes aegypti* (Culicidae) (Davis and Sokolov 1976), implying that it interfered with the detection of, and response to, host attractant compounds (Davis 1985). However, behavioral observations still suggested that DEET acted as a repellent (Boeckh et al. 1996; Hoffmann and Miller 2003), even in the absence of lactic acid. More recently, Ditzen et al. (2008) suggested that DEET interfered with the response of the malaria mosquito, *Anopheles gambiae* (Culicidae), to the host attractant compound 1-octen-3-ol. Their conclusion was based on an experimental artifact pointed out by Syed and Leal (2008), who demonstrated that combined stimulus delivery as done by Ditzen et al. (2008) causes a reduction in odorant delivery. Therefore, the observed reduced physiological responses were not due to blocking of the olfactory system by DEET, but merely because less amount of odorant was delivered. In addition, Syed and Leal (2008) showed that DEET is detected by a specific ORN on the antennae of *Cx. quinquefasciatus* mosquitoes (Culicidae), and that it is not a blocker of ORNs for other compounds. Furthermore, DEET was shown to be an active repellent for sugar-seeking male and female mosquitoes, and caused reduced landing of females in the vicinity of an attractive, warm, black surface (Syed and Leal 2008). This recent discovery of a specific ORN for DEET, along with its olfactory sensitivity to plant essential oil components, suggests that novel repellents with enhanced activity or longevity, such as those derived from botanical materials, can be discovered in a rational manner through the use of the DEET ORN as an electrophysiological screening tool (Pickett et al. 2008), i.e., by assessing their ability to activate the DEET ORN in a similar manner to DEET itself. This approach has the potential to be extended to ORNs for other repellents, once a specific ORN has been characterized. (Fig. 1).

Non-host Species The response of vectors to compounds from related non-host species is considered more adaptively valuable in their behavioral ecology than the response to botanically-derived repellents. Although there are plenty of anecdotal data to support this, scientific evidence is scarce.

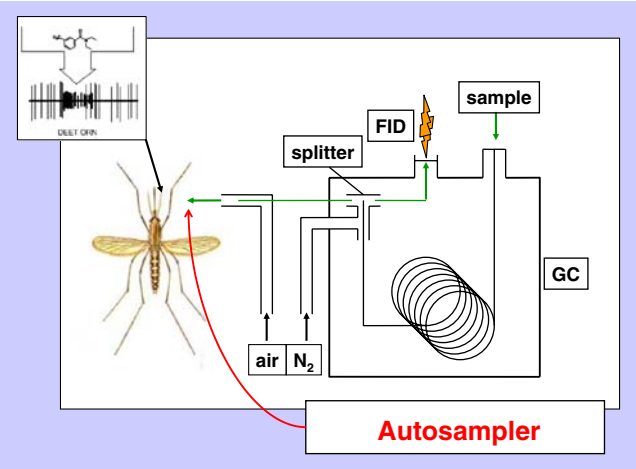

Fig. 1 Active compounds in samples from naturally repellent sources can be identified by gas chromatography (GC)-coupled electrophysiology. By replacing the GC with an autosampler and using a single olfactory neuron (e.g. one which responds to a known plant repellent and also responds to a synthetic repellent such as DEET or a repellent insecticide) compound libraries could be screened for new types of repellent

Evidence is provided, however, from the Morsitans group of tsetse flies, *Glossina* spp. (Glossinidae) that transmit trypanosomiasis (nagana) in cattle (Bovidae). Here, elegant chemical ecological studies have shown that the vertebrate non-host waterbuck, *Kobus defassa* (Bovidae), produces potent non-host repellents for this group of flies (see section below on Afro-tropical vectors). The hypothesis that underpins this work has allowed development of repellents in aquatic ecosystems, for example against the salmon louse, *Lepeophtheirus salmonis* (Copepoda: Caligidae), a major arthropod pest that affects farmed and wild Atlantic salmon, *Salmo salar*, (Salmonidae) populations (Bailey et al. 2006; Mordue (Luntz) and Birkett 2009). It was shown that the non-host fish, the turbot, *Scophthalmus maximus* (Scophthalmidae), produces two compounds, 4-methylquinazoline and 2-aminoacetophenone, which when added to salmon (host)-conditioned seawater, interfere with *L. salmonis* host-seeking behavior (Bailey et al. 2006). Although unclear in this scenario, certainly for Dipterous flies, it is still possible for hosts to be detected in the presence of non-host species. For example, human beings are located easily by anthropophilic mosquitoes such as *An. gambiae*, even when surrounded by cattle (Costantini et al. 2001).

Host Derived Repellents Individuals within an animal population can be extremely unattractive, even to arthropods highly adapted to those species. Similar to the situation for related non-host species described above, there have been plenty of anecdotal accounts to support this hypothesis, but again only recently has evidence been provided on a scientific basis, specifically for Diptera. For dairy cattle, the loading of nuisance and pathogen-vectoring cattle flies (Muscidae) is uneven across a herd of same-breed individual heifers, *Bos taurus* (Jensen et al. 2004; Oyarzun et al. 2009), with the hypothesis being that differential fly-loads are mediated by volatile semiochemicals. Subsequent studies have shown that reduced fly-loads are due to the enhanced production and release of 6-methyl-5-hepten-2-one (MHO), and that addition of slow-release formulations that release this compound to "attractive" cattle could reduce fly loads (Birkett et al. 2004). The presence of "inappropriate" host signaling has been investigated in human beings. Field studies using odor-baited entry traps (OBETs) have shown that the addition of human-specific compounds (*E*)-, (*Z*)-3-methyl-2-hexenoic acid and 7-octenoic acid, major components of human axillary sweat, significantly reduce trap catches of *Anopheles gambiae* s.l. (Costantini et al. 2001). The differential attractiveness of human beings to mosquitoes (Culicidae) and biting midges (Ceratopogonidae) has been studied extensively (Logan et al. 2008, 2009). For the yellow fever mosquito, *Aedes aegypti*, and the Scottish biting midge, *Culicoides impunctatus*, differential attraction has been demonstrated and shown to be due to the presence of enhanced "inappropriate" host signaling, mainly *via* MHO, geranylacetone, octanal, nonanal, and decanal. The ability to reduce upwind flight activity of *Ae. aegypti* by using nanogram levels of compounds is indicative of how such signaling is adaptively valuable in the host-seeking ecology of this mosquito species (Logan et al. 2008, 2009).

Host-Derived Attractants and Attractant Pheromones

For the control of pathogen vectors, host-derived attractants and attractant pheromones can be exploited further by combined use of trapping with repellents as part of a push-pull strategy (Cook et al. 2007; Logan and Birkett 2007; Hassanali et al. 2008). Many pathogen vector species respond to attractants that are derived from host excretory products, such as urine, dung, exhaled breath, and skin secretions, including CO_2, lactic acid, ammonia, acetone, and fatty acids (Logan and Birkett 2007). Studies on the Morsitans group of tsetse flies, *Glossina* spp., (Glossinidae), have identified kairomones from cow odors (Hall et al. 1984) and urine (Owaga et al. 1988). These have been used in baited traps and targets for effective suppression of *Glossina* spp. populations (e.g., POCA; 3-n-Propylphenol: 1-Octen-3-ol: *p*-Cresol: Acetone) (Vale et al. 1988; Brightwell et al. 1991). However, such blends appear to be partially attractive, compared to natural host (cattle) odor, implying that other attractants need to be identified in order to provide full activity.

Pheromones, which although not always directly related to the vectoring component of the pathogen vector life-cycle, are highly species-specific, and, therefore, offer a potent means of vector control, through their deployment in trapping systems. Examples of pheromones for vectors are rare, but *Culex* spp. mosquitoes that are responsible for the transmission of West Nile Virus along with other viruses, and filarial nematodes, utilize an oviposition pheromone, (5*R*,6*S*)-6-acetoxy-5-hexadecanolide, to assess the suitability of an oviposition site (Laurence and Pickett 1982, 1985). This pheromone, which is released from the apical droplets of egg rafts, has been tested successfully in many field trials in several countries in afflicted regions (Otieno et al. 1988; Mboera et al. 2000a, b), and now is commercially available for trapping systems. The pheromone can be deployed effectively if used in conjunction with environmentally benign larvicides, such as the insect growth regulator pyriproxyfen or larvae-specific pathogens such as the fungus *Lagenidium giganteum* Couch (Pickett and Woodcock 1996). Use of the pheromone in such circumstances is tempered by three factors.

First, optimal activity requires use in conjunction with site-derived oviposition cues such as 3-methylindole (skatole), which is derived from stimuli such as decaying organic material or pit latrine water (Mordue (Luntz) et al. 1992; Blackwell et al. 1993; Mboera et al. 2000a), or other compounds such as trimethylamine and nonanal, which also are generated by decaying food material (Leal et al. 2008).

Second, *Culex* spp. mosquitoes habituate to local oviposition site cues. This was illustrated by the adaptation of mosquitoes based at the London School of Hygiene and Tropical Medicine to local, i.e., London, tap water (Pickett and Woodcock 1996). Thus, it appears that local oviposition cues need to be identified prior to their local application. While this may seem initially to be technically challenging, the development of new analytical techniques, e.g., stir bar sorptive extraction (SBSE), offers opportunities for rapid identification of further oviposition cues (Carson et al. 2009).

Third, the production of pheromone for their deployment, while being affordable in developed countries, represents a financial and technical challenge for local production. Thus, higher plants offer alternative, cheap, and renewable resources for production of pathogen vector pheromones in afflicted countries. These include production of the *Culex* spp. oviposition pheromone from the seed oil of *Kochia scoparia* (Chenopodiaceae) (Olagbemiro et al. 1999, 2004), and the sandfly, *Lutzomyia longipalpis*, pheromone, (*S*)-9-methylgermacrene-B, from the essential oil of *Geranium macrorrhizium* (Geraniaceae) (Hooper et al. 2006).

Host Shifts in Pathogen Vectors

Studies on the semiochemicals produced by human and birds hosts of *Culex* spp. mosquitoes revealed that one compound, nonanal, is a significant component of human, pigeon (*Columbia livia*), and chicken (*Gallus gallus*) odor (Syed and Leal 2009). Furthermore, this compound, along with others in host odor, is detected with extreme sensitivity by ORNs on the antennae of *Cx. quinquefasciatus*. Nonanal was detected by a large array of sensilla, and was by far the most potent stimulus. It has been suggested that *Cx. quinquefasciatus* can detect humans and birds, thereby facilitating host shifts, and thus, transmission of West Nile virus among human populations (Syed and Leal 2009). In field experiments, a combination of nonanal and CO_2 acts in a synergistic manner, leading to significantly higher catches of *Culex* mosquitoes in binary traps, compared to individual traps (Syed and Leal 2009).

Molecular Recognition Processes Underlying Pathogen Vector Behavior

The mechanisms that underlie olfactory reception of semiochemicals by insects currently are receiving much attention, with a view to providing new opportunities for pest control, including pathogen vectors. These are primarily targeted at two levels, odorant-binding proteins (OBPs) and olfactory receptors (ORs).

Odorant-binding proteins have been proposed as key agents involved in the movement of semiochemicals across the antennal sensillum lymph towards ORs (Pickett et al. 2009). Genes and cDNAs encoding the OBPs of a number of insect species have been cloned, including pathogen vectors, and recombinant OBPs that have been generated *via* suitable expression systems. The first OBP to be isolated from a mosquito was from *Cx. quinquefasciatus* (Ishida et al. 2002). Subsequent immunohistochemistry studies have shown that this OBP, termed CquiOBP1, is expressed in trichoid sensilla on the antennae that house an ORN sensitive to the oviposition pheromone, (5*R*,6*S*)-6-acetoxy-5-hexadecanolide (Leal et al. 2008). Furthermore, CquiOBP1 exists in monomeric and dimeric forms, with the monomer binding the oviposition pheromone in a pH-dependent manner, with a change in pH resulting in an apparent loss of binding due to changes in secondary structure (Leal et al. 2008). Interestingly, binding studies with enantiomers of the pheromone have shown that the non-naturally occurring antipode have higher affinity than the natural stereoisomer. Since the initial isolation of CquiOBP1, similar OBPs have been isolated from other *Culex* spp., including *Cx. tarsalis* (Ishida et al. 2003), *Cx. pipiens* and

Cx. molestus (Leal et al. 2008). cDNAs for putative OBPs have been isolated from *An. gambiae* (Biessmann et al. 2002).

The availability of genome sequences for mosquitoes has enabled the identification of genes that encode putative OBPs *via* genome and EST database searches. Their expression is detected in antennae by using quantitative real time PCR, and their production by using recombinant technology. These include genes for so-called "Plus-C" OBPs in *An. gambiae* (Zhou et al. 2004), genes for OBPs in anthrophilic *An. gambiae* s.s. and zoophilic *An. arabiensis* (Li et al. 2005), *Ae. aegypti*, and *An. gambiae* (Zhou et al. 2008), and for *Cx. quinquefasciatus* (Pelletier and Leal. 2009). Despite the discovery of putative OBPs for these pathogen vectors and other insects, the molecular recognition processes that involve OBP binding of semiochemicals are yet to be elucidated, Thus, experimental approaches are required that allow measurement of binding and specificity. To this end, several techniques have been developed to measure the non-covalent interaction between OBPs and semiochemicals. These include: (1) fluorescence binding assays, which have been used most recently to study the binding properties of OBPs from *Ae. aegypti* (Li et al. 2008) and the silkworm moth, *Bombyx mori* (Zhou et al. 2009), (2) cold-binding assays, which have been used to study the interaction between native and mutated pheromone-binding proteins (PBPs) from *B. mori*, and the pheromone bombykol (Leal et al. 2005), and (3) electrospray ionization mass spectrometry (ESI-MS), which was used to study the interaction between the *B. mori* pheromone-binding protein BmorPBP1 and bombykol (Oldham et al. 2000). Recently, high-throughput ESI-MS analysis of BmorPBP1 incubated with its' pheromone components (bombykol and bombykal) and analogues has been developed (Hooper et al. 2009). The availability of a high-throughput assay would allow *in vitro* screening of OBPs against compounds identified as pathogen vector semiochemicals, and would provide a means of searching libraries of compounds for new semiochemicals with enhanced activity. However, despite evidence that OBPs appear to be abundant in pathogen vectors and have the potential to be used in their control, functional evidence for the role of OBPs in mediating odor selectivity is still quite sparse, and *in vivo* evidence of their role is required. Studies on insect ORNs (see below) by Carlson and co-workers have apparently shown that ORNs are not matched to their cognate OBPs. This led to a suggestion that OBPs do not play a large role in specifying odor selectivity or sensitivity, at least in *Drosophila melanogaster*.

The identification and functional characterization of ORNs in pathogen vectors also offers new opportunities for control. The peripheral receptor system for *Cx quinquefasciatus*, i.e., maxillary palps and antennal ORNs, has been mapped, with all the sensilla on the palps being shown to house 3 ORNs and respond to CO_2 and plant/floral odors (Syed and Leal 2007). Antennal ORNs were shown in later studies to respond to a variety of chemicals (Syed and Leal 2009). High throughput electrophysiological assays have been used to identify volatile compounds that activate, inhibit, or block ORNs for *D. melanogaster*, with active compounds being tested for behavioral activity (Hallem and Carlson 2006; Kreher et al. 2008). Specialized ORNs that mediate the detection and avoidance of CO_2 have been identified in *D. melanogaster*, and recent studies by Turner and Ray (2009) have proposed that this phenomenon is due to inhibition of the CO_2 ORNs by volatile compounds present in food odor. The authors also report similar inhibition of CO_2 ORNs in *Culex* spp. mosquitoes, and highlight the important role that appropriate inhibitory odorants could have in disrupting CO_2-mediated host seeking behavior in pathogen vectors (Turner and Ray 2009). Similar to the OBP story, this approach potentially can be applied to search for new semiochemicals with superior activity. However, as peripheral responsiveness to stimuli must be integrated by the organism to mediate behavior, this suggests a potential limitation in developing such a strategy.

New Chemical Ecology Studies on Afro-Tropical Pathogen Vectors

The impact of pathogen vectors upon livestock and human health is greatest in sub-Saharan African countries. Chemical ecological research in these countries has been dominated by studies on the attraction of the Morsitans group of *Glossina* spp. tsetse flies, and *Anopheles* / *Culex* spp, mosquitoes to host odors and oviposition cues, as exemplified elsewhere in this review. Nevertheless, novel research is being undertaken that aims to identify: (1) semiochemicals from non-hosts that can be developed for livestock protection, (2) semiochemicals from hosts for the control of vectors of neglected diseases that can be deployed in the protection of livestock belonging to resource-poor farmers, e.g., nomadic communities, who are unable to access more advanced approaches to pathogen vector control, and (3) novel oviposition semiochemicals.

While host-derived attractants have been identified for the Morsitans group of *Glossina* spp. from host breath and urine (see above), more recent studies have focused on feeding preferences, including the existence of non-host allomones produced by the non-preferred host waterbuck, *K. defassa* (Gikonyo et al. 2000). Analysis of the odor composition of preferred (buffalo, *Syncerus caffer*, and ox, *Bos indicus*) and non-preferred (*K. defassa*) species, and electrophysiological studies, have shown that the odors of the two preferred hosts are comparable. They comprise medium-chain, saturated or unsaturated aldehydes and

phenolic compounds, with the non-host odor containing fewer aldehydes but more phenolic components and a series of 2-ketones (C_8–C_{13}) and δ-octalactone, and moderate amounts of C_5–C_9 straight chain fatty acids. The electrophysiological responses of *Glossina* spp. show that 2-ketones and the lactone from the non-host odor are physiologically active (Gikonyo et al. 2002). Subsequent behavioral studies have shown that when presented with EAG-active components found specifically in the non-host odor, typical upwind flight behavior of flies is disrupted, with flies avoiding the non-host blend (Gikonyo et al. 2003). The behavioral responses of *Glossina* spp. to putative repellents based on guaiacol (2-methoxyphenol), a known mild repellent, also have been investigated, with the aim of identifying analogues with more potent repellent activity (Saini and Hassanali 2007). Of the compounds tested, the 4-methyl-substituted analogue (4-methylguaiacol) elicited stronger repellent effects, compared with guaiacol. Furthermore, the 4-methyl derivative reduced significantly trap catches of attractant-baited traps, and when applied to ox hosts, reduced the proportion of flies feeding on the host. Application of the repellent to approximately 75% of cattle herds has been shown to protect entire cattle herds (Saini and Hassanali 2007).

The Palpalis group of tsetse flies are responsible for the transmission of Human African Trypanosomiasis (HAT) across sub-Saharan Africa. In order to develop cost-effective control methods for *Glossina fuscipes* spp., the most important HAT vector, the responses of *G. fuscipes fuscipes* to host odors have been investigated in Kenya. Field trapping studies showed that odors from the monitor lizard, *Varanus niloticus*, significantly increased landing responses from *G. f. fuscipes* compared to ox and human odor, thereby suggesting that attractants in the lizard odor can be exploited in developing traps for controlling this major HAT vector (Omolo et al. 2009).

The oviposition behavior of gravid *An. gambiae* mosquitoes, in response to quality of oviposition site water and the density of larvae already at the site, has been investigated. The presence of larvae in distilled water deterred oviposition, but in natural breeding site water, a low density of larvae increased oviposition, whereas a higher density inhibited oviposition. These data suggest that a volatile pheromone is emitted by conspecific larvae, and that a non-olfactory cue deters oviposition at sites with high larval densities (Sumba et al. 2008).

Future Directions

For any vector-borne pathogens, the incidence and prevalence of pathogen infection in animals and human beings is dependent upon the distribution and abundance of their vectors. Thus, climate change, resulting in the movement and spread of pathogens and their vectors, undoubtedly will play a major role in affecting the distribution of diseases transmitted by pathogen vectors. This has been illustrated recently by the movement of Bluetongue virus (BTV), an arboviral pathogen that affects ruminants, which is spread by *Culicoides* spp. biting midges (Ceratopogonidae). After emerging in Northern Europe in 2006, this pathogen spread to populations across several European countries due to enhanced ambient temperatures and into the United Kingdom in 2007 (Purse et al. 2005; Carpenter et al. 2008). Transmission of BTV is thought to be due to *Culicoides* spp. (*C. obsoletus* and *C. pulicaris*) (Carpenter et al. 2008), but in order to provide accurate surveillance of such species in farmed livestock, which is a fundamental requirement of understanding the arbovirus epidemiology, reliable, optimized trapping systems that incorporate semiochemicals are required (Carpenter et al. 2008). Another striking example of the influence of climate change upon the incidence and prevalence of pathogen infection is the emergence in southern Europe in 2007 of Chikungunya fever, a disease affecting humans that is caused by an arboviral pathogen (Angelini et al. 2007). Although this pathogen originally was endemic to Africa, South-East Asia, and the Indian continent, its detection in European populations of *Ae. albopictus* suggests that it has adapted to enhanced ambient temperatures in southern Europe. Thus, as for other pathogen vectors, the behavioral and chemical ecology underlying host location must be elucidated so that semiochemicals for use in trapping systems for population monitoring and control become available.

Pheromones (sex, aggregation, and oviposition), which although not always directly related to the pathogen transmission stage of the life cycle, also can be incorporated into optimized trapping systems. Although the underlying mechanisms associated with the chemical ecology of oviposition behavior have been studied extensively for *Culex* spp. mosquitoes, e.g., the oviposition pheromone and site-derived cues, such mechanisms need to be appropriately investigated for other vector species.

As stated above, host-derived attractants, and pheromones, can be used in trapping systems for vector population monitoring and control. However, their potential can be fully realized only when used in conjunction with repellents for livestock and human protection. The identification of host-derived repellents, as exemplified by the discovery of 6-methyl-5-hepten-2-one and geranylacetone from human beings (Logan et al. 2008), potentially will provide a new class of repellents that are highly active due to their ecological role in non-host avoidance. Deployment of such repellents that use slow-release formulations is technically challenging, but the availability of novel dispenser technologies will facilitate their commercial

development. A more sustainable approach is to enhance the production of repellents in hosts, by exploring their biosynthesis, and therefore, the genetic factors that are responsible for repellent production.

In addition to identifying new semiochemical tools for improved trapping systems, investigations into the olfactory processes that underlie the perception of semiochemicals also will potentially provide opportunities for improved detection of pathogen vectors, through the development of biosensors based either on whole insects, e.g., honeybee, *Apis mellifera*, olfaction (Pickett et al. 1998), or on over-expressed insect OBPs or ORs. Furthermore, the development of physical sensors such as portable, miniature mass spectrometers, for the detection of pathogen vector semiochemicals also provides a potential route to improved vector detection (Birkett and Pickett 2006).

In summary, in a changing global climate, the movement of vector-borne pathogens requires generation of additional scientific knowledge surrounding their chemical ecology. New and efficient tools for population monitoring and control will be needed that will both be acceptable to the general public, and affordable even to the poorest of communities in afflicted regions. This will be a grand challenge, on a global scale, for chemical ecologists in the 21st century.

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