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Insect pheromones: An overview of function, form, and discovery

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For many species of insects, lipid pheromones profoundly influence survival, reproduction, and social organization. Unravelling the chemical language of insects has been the subject of intense research in the field of chemical ecology for the past five decades. Characterizing the forms, functions, and biosynthesis of lipid pheromones has led not only to the development of strategies for controlling agricultural pests but has also provided insights into fundamental questions in evolutionary biology. Despite the enormous variety of chemical structures that are used as pheromones, some common themes in function and biosynthetic pathways have emerged across studies of diverse taxa. This review will offer a general overview of insect lipid pheromone function and biochemical synthesis, describe analytical methods for pheromone discovery, and provide perspectives on the contribution of chemical ecology to pest control and understanding evolutionary processes.

1. Introduction

Pheromones are chemical signals used for communication between members of the same species. Some of the most important decisions made by organisms are mediated by pheromones. Many of these signals, particularly those produced by insects, are lipid molecules. Among the numerous roles that have been elucidated for pheromones include attraction, aggression, aphrodisiacs, anti-aphrodisiacs, aggregation, kin recognition, and alarm signaling. So pervasive are these molecules that a number of organisms mimic the chemical language of insects in order to lure prey or unwitting pollinators. For example, predatory bolas spiders emit the same sex attractant signals used by moths to ensnare the moths at close range by swinging a bola of silk [1]. In addition, some varieties of orchids both look and smell like different species of moths to attract pollinators [2]. Since the discovery of the first pheromone in 1959, the field of chemical ecology has rapidly progressed with the incorporation of methods from multiple scientific fields including analytical chemistry, neurophysiology, and genetics. This interdisciplinary approach has allowed our understanding of pheromone detection and behavior to be distilled down to the level of discrete neural circuits [3–5]. Additionally, discoveries in chemical ecology are now routinely applied to manipulate the behavior of agricultural pests and disease-bearing insects [6]. This review will offer a general overview and summarize recent findings on lipid pheromone function, structural diversity, biochemical synthesis, as well as the methods used for pheromone discovery. We will also provide perspective on the utility of pheromone biology in agricultural pest management and show examples of how comparative studies of pheromone systems have provided insights into the broad field of evolutionary biology.

Abbreviations: CHC, cuticular hydrocarbon; QMP, queen mandibular pheromone; DART, direct analysis in real time; ESI, electrospray ionization; GC–MS, gas chromatography–mass spectrometry; GC EAD, gas chromatography electroantennogram detection; LDI, laser desorption ionization; NMR, nuclear magnetic resonance.

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Trivial and systematic pheromone names

Blattellaquinone (3,6-dioxocyclohexa-1,4-dien-1-yl)methyl-3-methylbutanoate
Bombykol (10*E*,12*Z*)-hexadeca-10,12-dien-1-ol
CH503 (3*R*,11*Z*,19*Z*)-3-acetoxy-11,19-octacosadien-1-ol
cis-Vaccenyl Acetate (cVA) (11*Z*)-octadec-11-en-1-yl acetate
Crematoenone (*E*)-1-((1R*,2R*,4aS*,8aR*)-2-(hept-6-enyl)-1,2,4a,5,6,7,8,8a-octahydro-naphthalene-1-yl)-but-2-en-1-one
Disparlure (7*RS*, 8*SR*)-7,8-epoxy-2-methyloctadecane
Exo-brevicomin (1*R*,5*S*,7*R*)-7-ethyl-5-methyl-6,8-dioxabicylo[3.2.1]octane
(*E*)-β-farnesene (6*E*)-7,11-dimethyl-3-methylenedode-1,6,10-triene
Frontalin (1*S*, 5*R*)-1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane
HDA (QMP component) (2*E*, 9*RS*)-9-hydroxy-2-decenoic acid
HOB (QMP component) methyl 4-hydroxybenzoate
HVA (homovanillyl alcohol QMP component), 4-(2-hydroxyethyl)-2-methoxyphenol
Ipsdienol (4*S*)-2-methyl-6-methyleneocta-2,7-dien-4-ol
Ipsenol (4*S*)-2-methyl-6-methylene-7-octen-4-ol
Japonilure (5*R*)-5-[(Z)-dec-1-enyl] oxolan-2-one
ODA (QMP component) (*E*)-9-oxodec-2-enoic acid
Sulcatol 6-methylhept-5-en-2-ol

2. Behavioral functions of pheromones

The term "pheromone" was originally proposed by Karlson and Lüscher in 1959 as "substances which are secreted to the outside by an individual and received by a second individual, in which they release a specific reaction". It is derived from two Greek words, *pherin* (to transfer) and *hormōn* (to excite) [7]. In the same year, Adolf Butenandt, a German biochemist who was awarded the Nobel Prize in Chemistry in 1939 (for the chemical synthesis of sex hormones), identified the first pheromone chemically [8]. Since then, numerous advances have been made in our understanding of the functional properties of pheromones.

2.1. Aphrodisiacs, attractants, and anti-aphrodisiacs

Pheromones play an important role in the reproductive behaviors of many insects. Chemical signals are used to recognize conspecifics (members of the same species), attract potential mates, indicate reproductive status, and advertise fitness. The first active pheromone was chemically identified in 1959 from the silkworm moth, *Bombyx mori* [8]. Named bombykol (Fig. 1), the attractant pheromone is emitted by females from a gland at the tip of the abdomen and advertises female availability and location. Remarkably, concentrations as low as 200 molecules/cm^3 (in the air) are capable of attracting males [9]. Initial characterization of bombykol required isolation from 500,000 female abdominal glands. Following fractional distillation, a diluted portion of each fraction was tested for its ability to induce a "flutter dance" response in the male. Current analytical instrumentation requires much less starting material for chemical characterization. However, the pairing of fractionation with a behavioral assay remains a common strategy for the identification of new pheromones.

In many dipteran species (e.g., house flies, fruit flies, vinegar flies, and mosquitoes), long chain dienes and monoene hydrocarbons found on the cuticular surface (cuticular hydrocarbons, CHCs) serve as attractants and aphrodisiacs that influence mate choice and induce courtship [10,11]. The first CHC pheromone identified from a dipteran species was (*Z*)-9-tricosene from the housefly, *Musca domestica*. This compound is found in the feces and cuticle of females and attracts males [12]. Synthetic (*Z*)-9-tricosene is commonly used as a bait in commercially available housefly traps [13]. Some of the same CHC signals used in mate selection are also important in species recognition. For example, cross species experiments using *Drosophila simulans* and *Drosophila sechellia* show that *D. sechellia* females "perfumed" with *D. simulans* CHCs induce courtship from *D. simulans* males [14].

CHCs can act as anti-aphrodisiacs as well and play an important role in preventing interspecies attraction. Experiments by Billeter et al. elegantly showed that female *Drosophila* which have been genetically manipulated to express very low levels of CHCs become attractive to males of other species [15]. This atypical cross-attraction is partly attributed to the absence of CHCs which normally inhibit courtship from other species but function as aphrodisiacs within the same species [16]. Interestingly, the linear alkene (*Z*)-7-tricosene (Fig. 1) has been identified as one of the signals which prevents interspecies courtship and establishes a species barrier between *Drosophila melanogaster* and other drosophilids. When the sensory receptor for (*Z*)-7-tricosene is genetically ablated in *D. melanogaster*, male flies are willing to court females of other species, despite obvious disparities in size and pigmentation. In this case, the absence of inhibitory signals overrides all other sensory cues in the decision to court [17].

In several species of bees, butterflies, and vinegar flies, anti-aphrodisiacs and courtship inhibitors are used by males to manipulate the behavior of other conspecific males [18–20]. For example, in *D. melanogaster*, the male-specific lipids cis-Vaccenyl Acetate (cVA) and (3*R*,11*Z*,19*Z*)-3-acetoxy-11,19-octacosadien-1-ol (CH503) are transferred from males to females during mating and inhibit courtship from subsequent courting males [21–23]. In other species of *Drosophila*, a complex mixture of male-produced triacylglycerides play a similar role (Fig. 1) [24]. This strategy benefits both males and females since potential competitors are dissuaded from inseminating mated females and females also spend less energy fending off unwanted mates.

Other than serving as "on" or "off" switches for mating, attractive pheromones can also function as nuptial gifts and signals that convey information about the quality of the sender. For example, pyrrolizidine compounds, which are toxic substances for many animals, are used by Arctiid moths in some cases as attractants for females and also as defensive compounds [25,26]. Males ingest alkaloids such as intermedine and lycopsamine (Fig. 1) from host plants and pass the compounds to females through direct contact with pheromone-infused abdominal brushes [27] and seminal infusion [28]. Females are attracted to males with higher titers since the pheromone offers the benefit of protection from predators not only for the females but also for her eggs. In addition to direct benefits, age and fertility are two other types of information that are conveyed by cuticular lipid pheromones. Kuo et al. showed that male *D. melanogaster* prefer younger females to older females and this decision is largely discerned through distinct age-related cuticular lipid profiles [29]. Similarly, females of the butterfly species *Bicyclus anynana*, also select mates on the basis of pheromone composition but prefer profiles correlated with mid-aged rather than younger males [30].

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