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Potential insight for drug discovery from high fidelity receptor-mediated transduction mechanisms in insects

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Abstract

Introduction—There is a pervasive and growing concern about the small number of new pharmaceutical agents. There are many proposed explanations for this trend that do not involve the drug-discovery process *per se*, but the discovery process itself has also come under scrutiny. If the current paradigms are indeed not working, where are novel ideas to come from? Perhaps it is time to look to novel sources.

Areas covered—The receptor-signaling and 2nd-messenger transduction processes present in insects are quite similar to those in mammals (involving G proteins, ion channels, *etc*.). However, a review of these systems reveals an unprecedented degree of high potency and receptor selectivity to an extent greater than that modeled in most current drug-discovery approaches.

Expert opinion—A better understanding of insect receptor pharmacology could stimulate novel theoretical and practical ideas in mammalian pharmacology (drug discovery) and, conversely, the application of pharmacology and medicinal chemistry principles could stimulate novel advances in entomology (safer and more targeted control of pest species).

Keywords

Drug discovery; Insects; Pheromones; Receptors; Second-messengers; Therapeutic targets

1. Introduction

We believe that an understanding of the chemical signaling in insects (not only pheromone delivery, but also other ligand-receptor kinetics and 2nd-messenger signal transduction) could provide insight into how evolution has addressed the need for extremely high selectivity and signal fidelity. This knowledge could be incorporated into the establishment and attainment of therapeutic targets and drug discovery efforts. The relative simplicity of insect ligand-binding systems could provide useful conceptual and experimental models for better understanding mammalian pharmacology (and novel drug-discovery efforts) and decrease the use of vertebrate animals. Conversely, pharmacologic principles could be applied to suggest the design of novel insect control strategies that would (i) be more selective and thus less toxic to non-target organisms, and (ii) replace current methods as they

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lose efficacy after evolution of insect counteradaptations. Some practical examples are delineated below.

Recent research has revealed significant similarities between chemical signaling systems in insects – including enantiomer-specific ligand binding and 2nd-messenger transduction (*e.g.*, [1–4]) – and the hormone/neurotransmitter pharmacology of mammals. Because of the large number and diversity of insect species, evolutionary pressures have created ligand(pheromone)-receptor binding interactions having extremely high affinity and selectivity. It would therefore seem that reciprocal benefits could be obtained from understanding common features of pharmacological and entomological systems [5, 6].

Insects produce a wide array of pheromones that perform a variety of functions, and these signals range from single- to multi-component systems. The detection of sex pheromones by male insects and selective response to only conspecific female emitters requires high-fidelity signal detection and transduction. It involves the discrimination of pheromone from irrelevant chemicals to which the sensors are exposed. In processes remarkably similar to mammalian ligand-receptor interactions, pheromone systems used by insects involve high-affinity, enantiomer-selective, antagonist-sensitive binding of ligand to specific binding sites.

To illustrate our point with an example, we selected the sex pheromone of gypsy moth (*Lymantria dispar* L.), because: (1) it provides a relatively simple model in that it utilizes a single-component pheromone, (2) its pheromone binds in a dose-related, enantiomer-selective, antagonist-sensitive manner to ionotropic and metabotropic protein ‘receptor’ sites, (3) the signal is transduced by mammalian-like 2nd-messenger systems, including G proteins, (4) the signal is transmitted *via* neuronal pathways to higher CNS centers, where afferent input is integrated and proper behavioral response coordinated, (5) it is an invasive species that poses serious environmental and economic threats.

Gypsy moth provides a relatively simple example, since it has one pheromone component, (7*R*,8*S*)-7,8-epoxy-2-methyloctadecane, named ‘disparlure’. The initial step involves dose-dependent, enantiomer-selective binding of (+) disparlure to specific proteins located within the hairs of the moth’s antennae. The pheromone is transported to primary afferent neurons, expressing ligand-gated ion channels and G protein-coupled receptors, which synapse on nerve clusters (ganglia) in the insect brain. Projection neurons transmit the signal to higher brain centers (protocerebrum) *via* antennocerebral tracts. Pheromone-receptor binding provides helpful insight into a phylogenetically conserved and integrated reception and 2nd-messenger mediated signal-response control system. Understanding of the pharmacology of this system and the remarkable degree of selectivity provided by a relatively simple compound structural spectrum could provide valuable insight into mammalian pharmacology and novel drug discovery efforts and, reciprocally, application of pharmacological principles for design of novel insect control strategies.

2. Representative example: Gypsy moth

Gypsy moth (*Lymantria dispar* L.) is indigenous to temperate forests of Europe, Asia, and North Africa. It was introduced into North America in 1869 near Boston when some escaped the laboratory of Étienne Léopold Trouvelot, who brought eggs from Europe with the intent of creating hybrids with native silk-spinning moths that would be cold hardy and less susceptible to native diseases. In the absence of major native predators, gypsy moths are now spreading west- and southward. They cause extensive damage to hundreds of species of trees and shrubs. Young caterpillars are covered by long ‘hairs’ and spin long silk threads that give them aerodynamic buoyancy, allowing them to be carried by wind (hence ‘gypsy’) and spread to nearby plants. If infestation is sufficiently intense, defoliation reduces

photosynthesis to an extent that it increases the plant's vulnerability to opportunistic fungi, other insects, and environmental stresses. Gypsy moth also poses human health risks [7].

Adult females of European ancestry do not feed or fly, and live only a few days. To reproduce, females must quickly attract a mate, relying on an airborne chemical lure (pheromone) for attraction (Fig 1A). Males detect this pheromone by a process that involves enantiomer-selective pheromone binding to protein receptors located in their antennae [8, 9] (Fig 1B). It is critical that the pheromone is species-specific in order to guarantee mating yet avoid detection by predators that exploit these signals to locate prey [10]. Mate location using chemical signaling in a heterogeneous chemical environment is especially challenging and mating success appears to be the most important factor affecting gypsy moth's rate of spread into new regions [11].

Numerous methods of control have been attempted [12]. Unfortunately, each has serious limitations: older pesticides adversely affected non-target wildlife; carbamates, organophosphates, and other acetylcholinesterase inhibitors are relatively nonselective, inhibiting the same enzyme in mammals and beneficial insects, including those that help control gypsy moth; Na^+ channel modifiers such as pyrethroids also are relatively nonselective, and growth inhibitors that interfere with exoskeleton development during molting are toxic to many beneficial insects and aquatic invertebrates, and so cannot be used near water. Attempts to establish Eurasian parasites (parasitoids) and predators, or exploit native species, have been partially successful in reducing the extent of outbreaks. The Asian fungus *Entomophaga maimaiga* is host-specific and exerts substantial mortality, but requires established populations (making it more suitable for reducing outbreaks than preventing spread) and sufficient rainfall (a largely stochastic element). Two other treatments include microbial pesticides: bacteria-produced insecticidal protein such as δ-endotoxin from the gram positive *Bacillus thuringiensis kurstaki* (Btk), and insecticidal virus such as nucleopolyhedrosis virus (NPV) introduced into sterile larvae and spread as a freeze-dried powder. *Bacillus thuringiensis* (δ-endotoxin) is activated in the alkaline environment of the gypsy moth's gut, where it lyses epithelial cells by forming cation channels that lead to larval death. While more selective than most synthetic pesticides, and compatible with the use of parasites, Btk is toxic to most Lepidoptera, which provide pollination and other valuable ecological services. NPV spreads rapidly within dense larval populations and is highly lethal. But the production process is currently time- and cost- intensive, so its use is restricted mainly to environmentally sensitive habitats. Another approach involves mimicking (for population monitoring) or disrupting (for preventing female location by males) pheromone signaling. Mating disruption is particularly effective at low population densities, and hence in areas into which gypsy moth is spreading. It is particularly well suited for environmentally sensitive areas, precisely because of the high specificity of signaling. Effective implementation requires an understanding of the composition of the signal and the nature of the signal sensing process. These are similar to chemical signaling systems in mammals (Table 1).

3. Pheromone signaling

3.1. Overview

Female gypsy moths synthesize and release pheromone, which is dispersed by the wind in heterogeneous plumes. Downwind conspecific males are able to detect small amounts of pheromone with sensory hairs (*sensilla trichodea*) located on their antennae. The antennae are relatively large compared to body size, highly branched (large surface area), and more structurally complex than those of the female. Dendrites of olfactory neurons within the hairs detect pheromone and transmit this information to alert the male to the presence of, and aid in navigation to, emitting female(s).

The dendrites are suspended in lymph. Pheromone is transported through the lymph by pheromone-binding proteins (PBP) having enantiomer-selective affinity, stimulates odorant-neuron dendrites, and is degraded by enzymes located in the lymph. Different binding sites, binding affinity, detection thresholds, and likely other factors, provide signal differentiation and message fidelity. The sex pheromone of *L. dispar* is (7*R*,8*S*)-7,8-epoxy-2-methyloctadecane ('disparlure') (Fig 2) [13, 14].

3.2. Composition and synthesis

Pheromone attraction has been demonstrated in over 1,600 species of moths, and where they have been identified typically consist of an 8 – 21 carbon chain with an alcohol, aldehyde, or acetate ester functional group. Many contain one or more double bonds, but the gypsy moth's does not. The female gypsy moth releases the (+)-stereoisomer of disparlure ((+)-disparlure), and is relatively unusual in utilizing only one pheromone component. The (−)-stereoisomer of disparlure does not attract males, and is considered an antagonist because racemic mixtures reduce trap catch. Biosynthesis of (+)-disparlure [15] starts in oenocytes (large secretory cells underlying the epidermis of the abdominal segments) where the carbon for the methyl-branched group is contributed by the amino acid valine. Carbon chain elongation, followed by Δ12 desaturation and decarboxylation results in the 19-carbon alkene 2-Methyl-Z7-octadecene (2Me-7-18:Hc). 2Me-7-18:Hc is transported to the pheromone gland (a specialized structure in females to produce and emit pheromone), where it is converted to the epoxide disparlure (mainly the *R*,*S* (−)-stereoisomer). Both enantiomers of disparlure have been synthesized *in vitro* using cross-metathesis of homoallylic alcohol derived from L-(+)-tartaric acid [16]. Several features of the chemical structure of disparlure are critical for pheromonal activity: two alkyl chains, *cis* conformation, methyl substituent at the C2 position, the position of the epoxide group, and chirality [14, 17]. This poses trade-offs for monitoring and control, because (+)-disparlure provides better activity, but the racemate is less expensive to synthesize.

Some species of insects share common molecules in their pheromone systems, which can cause partial overlap of activity in monitoring or control programs. In such cases, full specificity arises from unique permutations that combine multiple-component ratios, isomerisms, and spatiotemporal incidence. Although our manuscript focuses on phylogenetic conservation of transduction mechanisms, there are instances of common pheromones being used across broad taxonomic groups. For example, frontalin and brevicomin, pheromones of several bark beetle species, also occur in the urine of female elephants and are putatively biosynthesized by similar pathways, the lepidopteran pheromone (*Z*)-7-dodecenyl acetate functions as a preovulatory female-produced pheromone affecting male elephants, and elephant urine also contains the aphid alarm pheromones (*E*,*E*)-α- and (*E*)-β-farnesene [18]. Presumably these common chemical signals arose from convergent evolution acting on the biosynthetic economies and physical properties of these compounds.

3.3. Delivery

After 2Me-7-18Hc is synthesized in and transported from the female's oenocytes to the pheromone gland, it is converted to disparlure and released. Movement of signals through open environments constitutes a major difference between pheromone communication and mammalian ligand-receptor interactions, and requires special adaptations. In a wind tunnel assay, the time-averaged EC50 of (+)-disparlure (concentration that elicited response within 20 s in 50% of males) was 2×10^{-17} g/cm^3 [19]. In nature, pheromone concentration is primarily determined by the rate of emission and turbulent dispersion. Females rhythmically protrude and retract their pheromone-emitting gland about once s^{-1} or longer intervals, creating a pulsatile release pattern. The plume's structure is mainly dictated by forces of

turbulent diffusion. Males zigzag in and out of the plume (inspiration for the Japanese term for this insect: ‘maimaiga’ or ‘dancing moth’) during upwind flight. The characteristics of a plume might enhance the signal-to-noise ratio, orientation cues, or distance estimation [20]. The manner in which visual feedback, wind direction, the presence of attractive odor, and neural processing operate to track irregularly concentrated plumes to their source is complex and only partially understood [21].

A widely used model of pheromone dispersion was that of Sutten [22] and references therein), which for the case of an elevated source is given by

$$C_{xyzh}=\frac{Q\exp\left(-y^2/C_y^2x^{2-n}\right)}{\pi C_yC_zUx^{2-n}}\left\{\exp\left[-\frac{(z-h)^2}{C_z^2x^{2-n}}\right]+\exp\left[-\frac{(z+h)^2}{C_z^2x^{2-n}}\right]\right\},$$

where C_{xzyh} is concentration of pheromone at point (xyz) downwind from a point source at height h, Q is rate of release, U is mean wind speed, C_y and C_z are horizontal and vertical diffusion coefficients, respectively, and n is a parameter dependent on vertical profile of wind velocity. An alternative is the Gaussian plume model [22], given by

$$C_{xyzh}=\frac{Q}{2\pi\sigma_y\sigma_zU}\left\{\exp\left[-\frac{y^2}{2\sigma_y^2}\right]\right\}\left\{\exp\left[-\frac{(z-h)^2}{2\sigma_z^2}\right]+\alpha\exp\left[-\frac{(z+h)^2}{2\sigma_z^2}\right]\right\},$$

where the diffusion coefficients (C) in the first equation are replaced by dispersion coefficients (σ) and α is a constant introduced to account for pheromone adsorption to the ground or other materials. Neither equation is totally adequate [22], but they form a basis for modeling; an important challenge is how best to integrate the variable spatial and temporal scales of molecular diffusion with existing knowledge of insect behavior [21].

Upon detecting pheromone, quiescent male gypsy moths initiate wing fanning, and active males change from appetitive to upwind flight. They display a zigzag path toward the source along the centerline of the pheromone plume, maintaining correct in-flight orientation by traveling upwind while appraising forward progress using visual cues [23]. Flight patterns are influenced by meteorological conditions, obstacles, and topographical features. Many insects show synergistic interactions between pheromones and volatile plant semiochemicals, but this has not been shown for gypsy moth, probably because its unusually broad host plant range renders this less practical than strictly pheromonally-based communication.

4. Receptology

4.1. Detection, integration, and discrimination

Axons of pheromone-sensing (olfactory) neurons from the moth’s antennae enter the brain near the optic lobes and pass into the antennal lobe (AL) [24] (Fig 3). The neutropil of the AL is organized in glomeruli (neuronal networks between the axon terminals of olfactory sensory neurons and the neuritis of interneurons). The glomeruli are anatomically and functionally similar to olfactory systems of vertebrates. Projection neurons in the AL serve as major relays that transmit olfactory information *via* several inner, middle, and outer antennocerebral tracts (ACT) to higher, mainly ipsilateral, brain centers located within the protocerebrum for integration and processing [24]. Two areas, the calyces of the mushroom bodies and the lateral horn, are multisensory integration centers and premotor area,

respectively, and are involved in odor discrimination, learning, and appropriate behavioral responses.

4.2. Enantioselective ligand-protein binding

Pheromone enters the antennae of male moths by passing through pores in the cuticle of single-walled hollow antennal hairs (sensilla trichodea). Within the aqueous content of the sensilla (sensillar lymph) the hydrophobic pheromone binds to abundant (mM concentration) pheromone-binding proteins [25] that are secreted into the space along with K^+. The pheromone-PBP complex is transported to the dendritic membrane [26] of the 2 – 3 'olfactory' nerves that project into the hollow space of each hair [27]. The slow depolarization characteristic of the electroantennogram is initiated at the outer dendritic membrane by odorant receptors (OR) that are expressed in different populations of neurons and sensilla [28].

The concentration of PBP in gypsy moth antennae is about 10 mM. Other protein-transporting proteins are located within sensillar lymph: general odorant binding proteins (GOBP) [29], chemosensory specific proteins (CSP) [30], and others. Also, the PBP might play additional roles. The affinity of these proteins for particular pheromone molecules provides a mechanism for identifying conspecific mates.

Two major PBP in gypsy moth have been identified, cloned, and sequenced [31]: PBP1, which displays a preferential binding affinity for (−)-disparlure, and PBP2, which displays preferential binding affinity for (+)-disparlure [9]. Both have molecular weights of 15 – 16 kDa, which is similar to the size of PBP of many other insects. They have six cysteine residues that are highly conserved among insect PBP [32]. Most PBP have a highly variable region that is suspected to be the site of pheromone detecting selectivity. There appears to be only one binding site per protein and no cooperativity [33].

Plettner *et al*. [9] studied the disparlure–PBP equilibrium binding interaction of radiolabeled (+), (−), and racemic disparlure to preparations of recombinant gypsy moth PBP1 and PBP2. Both the association and dissociation processes of the disparlure–PBP interaction gave linear plots. However, it was not possible in this assay to vary the disparlure concentration over a sufficiently broad range to obtain meaningful (*i.e*., linear) Scatchard plots. The authors were still able to obtain estimates of the equilibrium binding constants (K_d values). PBP2 has an approximately 2-fold greater affinity for (+)- disparlure than (−)-disparlure (1.8 *vs* 3.2 μM, respectively), whereas PBP1 had an approximately 3-fold greater affinity for (−)-disparlure than (+)-disparlure (2.2 *vs* 7.1μM, respectively).

Gong *et al*. [8] found that the kinetics of the disparlure–PBP2 binding interaction is best modeled as a two-step process. The first is the non-(+)/(−)-disparlure selective uptake of hydrophobic disparlure from the buffer, a process that mainly involves the C-terminal region of PBP2. The second step involves enantiomer-selective fitting of disparlure ((+) > (−)) into the PBP2 binding pocket located in the core of the protein. The measured K_d of the (+)-disparlure–PBP interaction was about 3 μM, similar to that of Plettner *et al*. [9]. The binding affinity of (+)-disparlure to a truncated form of PBP2 lacking the 17 residues from the C terminus is 5 – 6-fold lower. The proposed model is

$$\mathrm{D+PBP2}\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}\mathrm{D}_{ex}\cdot\mathrm{PBP2}\underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}}\mathrm{D}\cdot\mathrm{PBP2}$$

where (+)-disparlure (D) initially rapidly associates with PBP2 at a site distal to the binding pocket (with forward and reverse rate constants k_1 and k_{-1}, respectively) to form an

intermediate complex (D_{ex}· BP2). This site possibly involves Trp37 in the α2-α3 loop, which is highly conserved in insect long-chain PBP. In the subsequent step, proper orientation and docking into the inner binding pocket of PBP2 results in the specific complex (D·PBP2) (with forward and reverse rate constants k_2 and k_{-2}, respectively).

At the dendrites of the afferent sensory neurons, the pheromone interacts with transmembrane G protein-coupled receptors (GPCR) that activate G_q and $G_{i/o}$→ phospholipase C → IP_3 [34–36] and other 2nd-messenger signal transduction cascades [37] that initiate an action potential *via* voltage-gated Na^+ channels (Fig 4). Recovery begins with an arrestin [38].

4.3. Signal clearance

Just as in mammalian ligand-receptor communication at synapses and other sites, the signal molecule must be continuously cleared in order to assure high signal-to-noise ratio (signal fidelity). Pheromones are cleared by degrading enzymes present in the lymph of the sensilla [39]. In gypsy moth the major mechanism of pheromone degradation involves enantioselective biotransformation. Catalyzed by epoxide hydrolase, (+)-disparlure is converted to (7*R*,8*R*)-*threo*-diol (97%) and a very small amount (about 3%) of (7*S*,8*S*)-*threo*-diol by addition of a water molecule to the oxirane ring (essentially the epoxide is converted to a hydroxide). The metabolites are behaviorally inactive. Since disparlure binding is mechanistically similar to ligand-receptor interactions in mammals, it would be interesting to know if disparlure produces related effects on mammalian physiology. To our knowledge, the only information relates to apparent lack of toxicity. Based on an anecdotal report [40], the pheromone possibly can persist in the human body at doses sufficient to attract males years after last exposure.

5. Synthetic analogs

Analogs of gypsy moth pheromone might serve as useful baits for sampling populations, or to interrupt males' reception of signaling in order to reduce populations or delay spread. For example, Solari *et al*. [41] synthesized a series of oxaspiropentane derivatives that differ from disparlure mainly by substituting a cyclopropyl group in place of either aliphatic chain (retaining the epoxide ring). Activity at the male olfactory apparatus was assessed by electroantennogram and behavior (*viz*., attraction). They identified both a mimic (agonist), 4-(1-Oxaspiro[2.2]pent-2-yl)butan-1-ol, that attracted males and an antagonist, 2-Decyl-1-oxaspiro[2.2]pentane, that inhibited (+)-disparlure activity. A series of individual and combinations of monoalkoxyphenols, dialkoxy- and dialkoxyally-benzenes, monoalkoxy allyl phenols, eugenols, and alkyl-eugenols were recently evaluated for efficacy (agonist or antagonist properties) on electroantennograms, and some showed activity [42]. In a subsequent study, Chen *et al*. [43] showed that some conformationally constrained mimics caused antennal depolarization indicative of additive or synergistic effects. Collectively, these results provide rationale to explore analogues as a way to increase bioactivity in the field.

6. Conclusion

Many insect pheromone molecules display dose-related, enantiomer-specific, antagonist-sensitive binding to ligand-gated and G protein-coupled receptors, and their transduction occurs *via* mammalian-like 2^{nd}-messenger pathways. The signal is transmitted along projection neurons to the insect's central nervous system, where afferent signal is integrated and the appropriate behavioral response is elicited. The ligand-interaction kinetics have been characterized and provides interesting insights into this phylogenetically conserved strategy of signal-reception and of an integrated signal-response control system. Recent advances

suggest potentially valuable and mutually beneficial cross-fertilization between pharmacology and entomology at both the basic scientific and translational application levels.

7. Expert opinion

There is an enormous diversity of insect pheromone systems. There are about 10 million species of insects and almost all utilize pheromones for a variety of purposes such as: long-distance attraction of mate (*e.g*., gypsy moth), short-distance or contact mate recognition (*e.g*., Asian longhorned beetle); aggregation (*e.g*., bark beetles); alarm (*e.g*., aphids); population size recognition (*e.g*., locusts); social caste differentiation (*e.g*., Hymenoptera); marking/spacing (e.g., parasitic wasps), and others. Many insects use several different types, and some use individual compounds for multiple functions. This yields an incredibly large array of chemicals that serve as pheromones and the requirement that pheromone-detection systems be sufficiently sensitive to discriminate between even closely related species. How this selectivity can be achieved with the seemingly simple chemical structures of most pheromones provides an intriguing challenge and stimulus for receptor theory and molecular modeling applications in pharmacology and medicinal chemistry. Some examples of specific information that could foster this integration include a better understanding of how genetic investment, and genetic variation, compare across different evolutionary lineages and among sensory modalities.

Natural pheromones of some insects outcompete currently available synthetic compounds, partly because of the higher number of point sources, and also because the complete natural blends are not always known, especially in systems where complex mixtures and plant chemicals interact. Similar complications can arise with moths, in which the ratio of females to baited traps can be very high, restricting the efficacy of pheromonally based control to low population densities. In such cases, more potent synthetic analogs in traps or selective antagonists of natural pheromones could potentially improve sampling accuracy and management. This has not been achieved to date. A consistent relationship between trap catch and actual abundance is desired for purposes of pest management, yet this sometimes differs among regions. It has been speculated that differences in temperature contribute to this variation, because temperature influences insect calling behavior and emission rates from a natural source or synthetic lure, yet these relationships are not necessarily identical. Integrative studies of the temperature-dependence of emission, plume movement and air-flow dynamics, pheromone-receptor equilibrium (thermodynamics) [44], and forward and reverse binding kinetics could be helpful.

In some systems pheromones have proven useful in ‘trapping out’ or disrupting the mating or aggregation of pest populations. However, the record of success of this approach is mixed, partly because deployed compounds are often not potent enough to override behavioral redundancies such as visual detection at high densities. The need for more effective behavior-modifying compounds is especially great for addressing non-native invasive insects or range expansions facilitated by climate change, because newly encountered plants lack coevolved resistance and predators complexes are lacking. Conversely, where pheromonal control works well, similar issues of biotype evolution could arise as with insecticides, and so new chemicals may be required. Despite the high selectivity of pheromones used by many insects, predacious and parasitic insects have decoded many of their chemical messages and use them to locate prey. ‘Trap-out’ programs can thus inadvertently remove many beneficial insects, thus diminishing their utility. Predator and prey behaviors are not totally congruent, however, because the former are constantly adjusting nuances of their signaling, at least within the constraints of maintaining intraspecific functionality [10]. These disparities provide opportunities for employing

pharmacological approaches to maximizing pest removal, while minimizing impacts on predators. Despite their limitations, insecticides remain a major means of controlling pest insects affecting human health and food supplies. Features of modern high-production intensive agriculture often render other tools inadequate. Insecticides are likewise often the only effective tools against damaging non-native insects being introduced in conjunction with increased global trade. Pharmacological approaches that judiciously exploit both the conserved and disparate features of signal-receptor interaction provide additional strategies for increasing efficacy while decreasing hazards to human health and environmental quality.

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Article Highlights

- The receptor-signaling and 2nd-messenger transduction processes in insects are quite similar to those in mammals.
- The detection of pheromone involves discrimination from irrelevant chemicals and selective response to only conspecific emitters.
- The evolutionary pressure has resulted in high-potency and high-fidelity receptor-mediated signaling.
- The high potency and selectivity provide a rich source of ideas and modeling for therapeutic targets.
- We propose that a better understanding of insect ligand-receptor processes could stimulate theoretical and practical advances in therapeutic targets and, conversely, the application of pharmacology and medicinal chemistry principles could stimulate novel advances in the discovery of safer and more targeted control of pest species.

Fig 1A

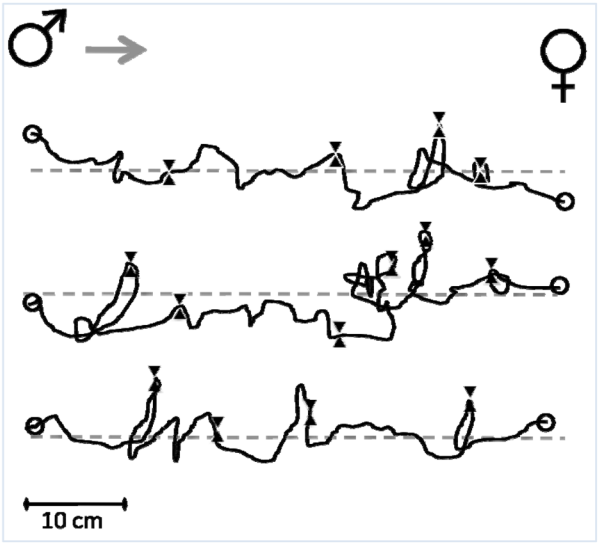

Fig 1B

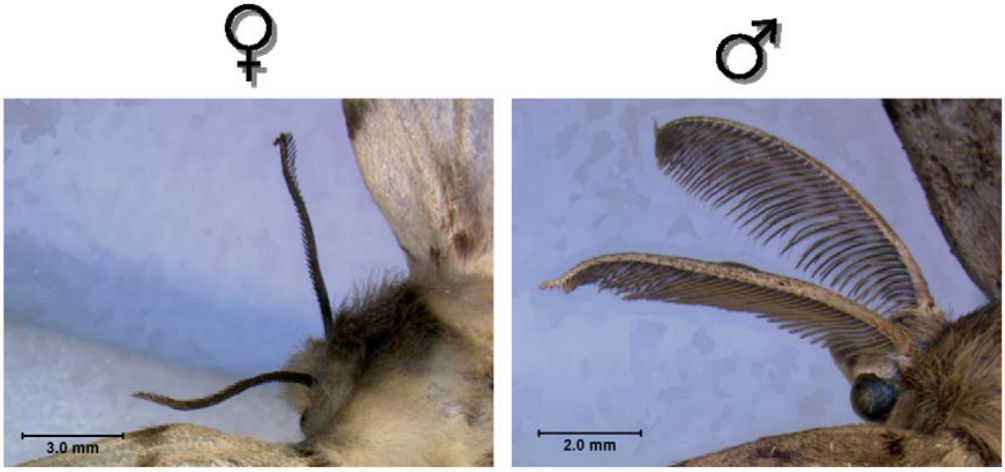

Fig 1.

A: Flight pattern of male gypsy moths in wind tunnel traveling up disparlure concentration gradient toward source.

B: Comparison of antennae of female and male gypsy moths (photo by Jesse Pfammatter, Department of Entomology, University of Wisconsin-Madison). Note: Females have an overall larger body than males.

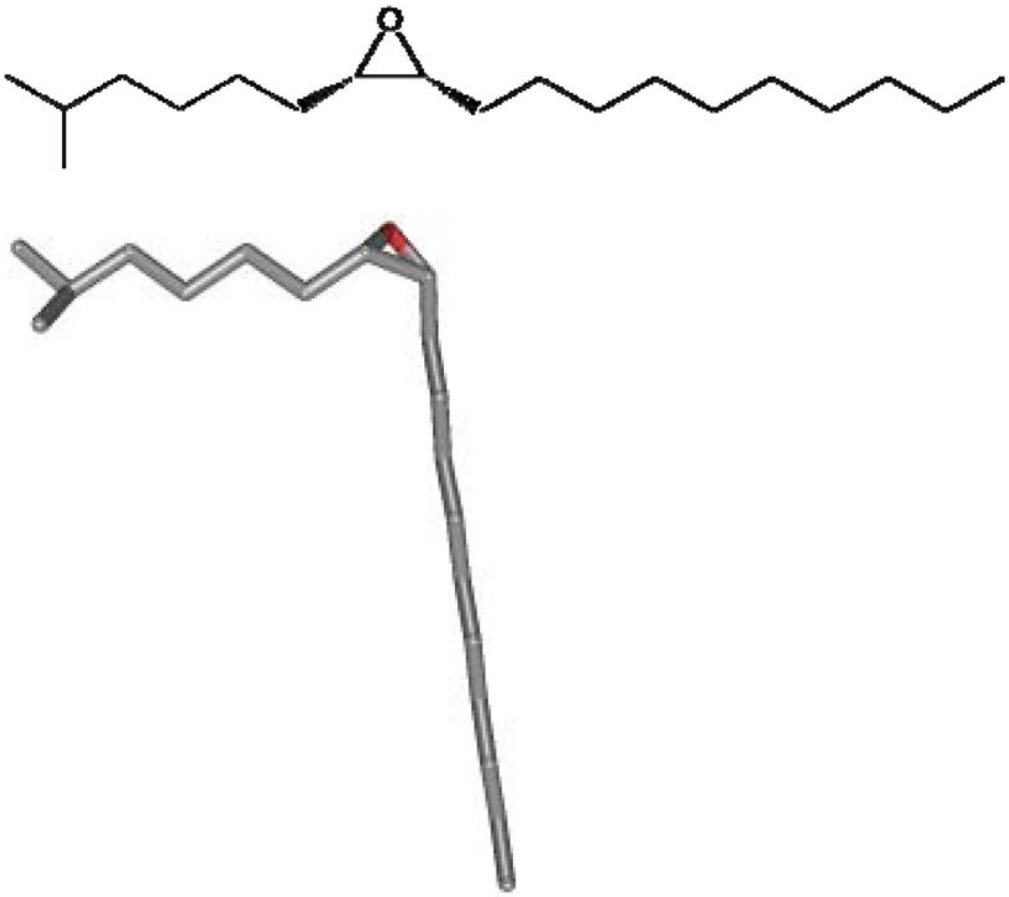

Fig 2.
2- and 3-D representation of disparlure.

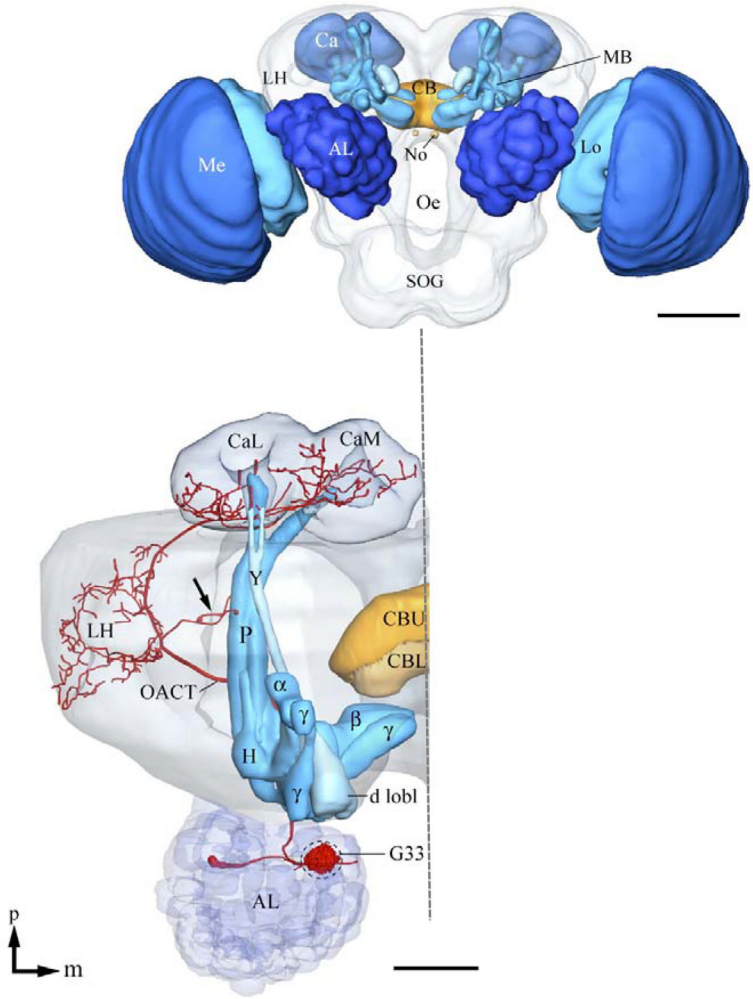

Fig 3.

3-D reconstruction of female moth brain (tobacco budworm) (frontal view above and expanded dorsal view below of glomerulus G33 and antennocerebral projection neurons leading to higher CNS centers. Scale bars = 200 μm (frontal), 100 μm (dorsal). Abbreviations as in original. From [24] with permission.

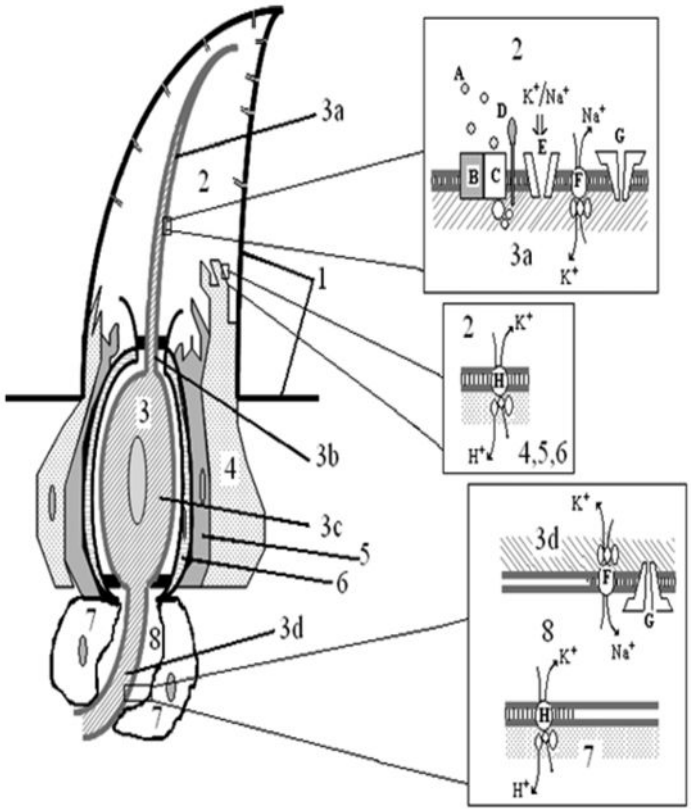

Fig 4.

Reprinted from [42] Copyright © 2010 American Chemical Society with permission: "Schematic diagram of a *sensillum trichodeum*: 1, cuticle (the cuticular wall of the sensillum has pores that end in pore canals); 2, sensillar lymph space [this compartment contains a solution rich in K+ and pheromone-binding protein (PBP, A in the top expansion window)]; 3, sensory neuron (3a, outer dendritic segment; 3b, inner dendritic segment; 3c, cell body; 3d, proximal axon segment); 4–6, accessory cells (4, tormogen; 5, tricogen; 6, thecogen) [thecogen, 6, envelopes the cell body and the inner dendritic segment; the space between the cell body, 3c, and the thecogen cell, 6, is separated from spaces 2 and 8 by tight junctions that are diffusion barriers for ions and other solutes (black bars)]; 7, glial cells (these cells envelope the axon); 8, perineurial space [this is found only between the proximal part of the axon and the glia; the expansion windows show known molecular components, relevant to this study, from the outer dendrite and sensillar lymph (top), the apical membrane of the accessory cells (middle), and the axonal/glial membranes (bottom)]; A, PBP; B, conserved receptor; C, olfactory receptor; D, sensory neuron membrane protein; E, ligand-activated monovalent cation channel; F, sodium/potassium ATPase; G, voltage-gated ion channel; H, V-type proton/potassium ATPase."

Table 1

Some commonality between insect and mammalian chemical signal processing.

Mammals	**Insects**
Odorant receptors in nose	Pheromone receptors in antennae
Plasma protein binding	Lymph protein binding
Dose-related response to ligand binding	Same
Requires high-fidelity detection	”
Requires ‘signal/noise’ discrimination	”
Receptor-mediated detection	”
– structure-activity relationship	”
– enantiomer-selective	”
– antagonist-sensitive	”
2nd-messenger transduction	”
– ionotropic (ligand-gated ion channels)	”
– metabolotropic (GPCRs)	”
Primary afferent neurons	”
Sensory ganglia	”
Projection neurons	”
Specialized sensory brain regions	”
Rapid clearance from receptors	”
Removal by metabolism	”