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Minireview

Scent of a Fly

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Sexual courtship is a highly ritualized behavior in many animals. Recent work in the vinegar fly, *Drosophila melanogaster*, has illuminated how the pheromone *cis*-vaccenyl acetate modulates sexual behavior in the fly. Chemosensory receptors and a sexually dimorphic circuit activated by this pheromone have been identified. This minireview highlights recent advances in the field of fly courtship.

What Is a Pheromone?

Before consummating the act, sexually reproducing animals need to answer a few critical questions. Beyond the problem of boy meets girl, the male needs to know whether the female is the same species, whether she is in fact female, whether she is fertile and receptive, and whether she has previously mated with a competitor. Females are also interested in the questions of species and gender, but are additionally concerned about the quality of the male. For many animals, answers to all these important questions can be gleaned simply by detecting chemical cues emanating from a prospective mate.

Pheromones, first identified in the silk moth almost 50 years ago (Butenandt et al., 1959; Karlson and Luescher, 1959), are chemicals released by members of the same species that elicit stereotyped behaviors (see Wyatt, 2003 for an excellent overview of this topic). Moths have solved the problem of detecting species, gender, and receptivity with a beautifully binary system (Hildebrand, 1995). Different moth species produce distinct pheromone blends, only receptive females emit pheromones, and only males detect female pheromones with specialized neurons on their antennae that express male-specific pheromone receptors (Figure 1A) (Sakurai et al., 2004). Thus, with this system, the questions of species, sex, and receptivity are answered simultaneously with one "sniff" by the male moth.

Bombykol, the pheromone that mediates silk moth sexual behavior, was purified from 500,000 female moths in 1959 (Butenandt et al., 1959). Since that time, the pheromone blends underlying sexual communication of many moths, beetles, cockroaches, and flies have been solved, and these compounds have proven to be economically valuable in suppressing insect populations via mating disruption—essentially leading males to believe there are females everywhere and interfering with the search for an authentic mate (Witzgall et al., 2008).

While moths have been the reigning paradigm for understanding pheromone detection for decades, in the last few years there has been much excitement over pheromone receptors, circuits, and behaviors in the vinegar fly *Drosophila melanogaster*. This human commensal insect has dominated developmental genetics for a century but was until recently thought to have a relatively impoverished system of volatile chemical communication. This minireview will discuss some highlights in the recent literature of *Drosophila* pheromone chemoreception and how this little insect is revealing some fundamental secrets underlying the processing of sexual cues.

A Fly Pheromone that Signifies Maleness

While cuticular hydrocarbons that modulate courtship behavior have been described in *Drosophila* for some time (Jallon, 1984), only one volatile pheromone acting via the olfactory system has been identified: 11-*cis* vaccenyl acetate (cVA). cVA is selectively produced by male flies (Bartelt et al., 1985; Ejima et al., 2007), but influences both male and female behavior. This pheromone induces aggregation of male and female flies (Bartelt et al., 1985; Xu et al., 2005), stimulates female receptivity toward males (Kurtovic et al., 2007), and suppresses male-male courtship (Kurtovic et al., 2007). While virgin females lack cVA, this male pheromone is transferred to females during mating, which may make them less attractive to other suitors (Ejima et al., 2007).

How can a single molecule elicit such very different behaviors in males and females? The sexually dimorphic behaviors could be encoded peripherally by differences in sensory neurons or centrally by sculpting sex-specific circuits. These possibilities have been examined in a spate of recent papers.

The Unique Design of an Insect Pheromone Receptor Signaling Complex: One or Several cVA Receptors?

While vertebrates sense pheromones with receptor proteins that differ from the odorant receptor (OR) superfamily (Mombaerts, 2004), insect pheromone receptors are now known to be encoded by selected members of the insect OR superfamily, a novel family of seven transmembrane receptor proteins (Robertson et al., 2003; Sakurai et al., 2004). The functional insect OR is a complex of a variable ligand binding subunit and a constant subunit called Or83b (Larsson et al., 2004; Nakagawa et al., 2005; Benton et al., 2006) (Figure 2). Intriguingly, insect ORs adopt a topology inverse to that of vertebrate ORs, which are G protein-coupled receptors, and instead seem to have the properties of odor-gated ion channels (Benton et al., 2006; Sato et al., 2008; Wicher et al., 2008). The extent to which heteromultimeric insect ORs—including those that sense pheromones—rely on G protein-coupled second messengers remains a controversial question (Gomez-Diaz et al., 2004; Kain et al., 2008; Sato et al., 2008; Smart et al., 2008; Wicher et al., 2008). It will be interesting to see this area mature in coming years.

Among the 62 OR genes in *Drosophila*, a single receptor, Or67d, was found to be highly selective for sensing cVA (Ha and Smith, 2006; Kurtovic et al., 2007; van der Goes van Naters and Carlson, 2007). Antennal lobe projection neurons

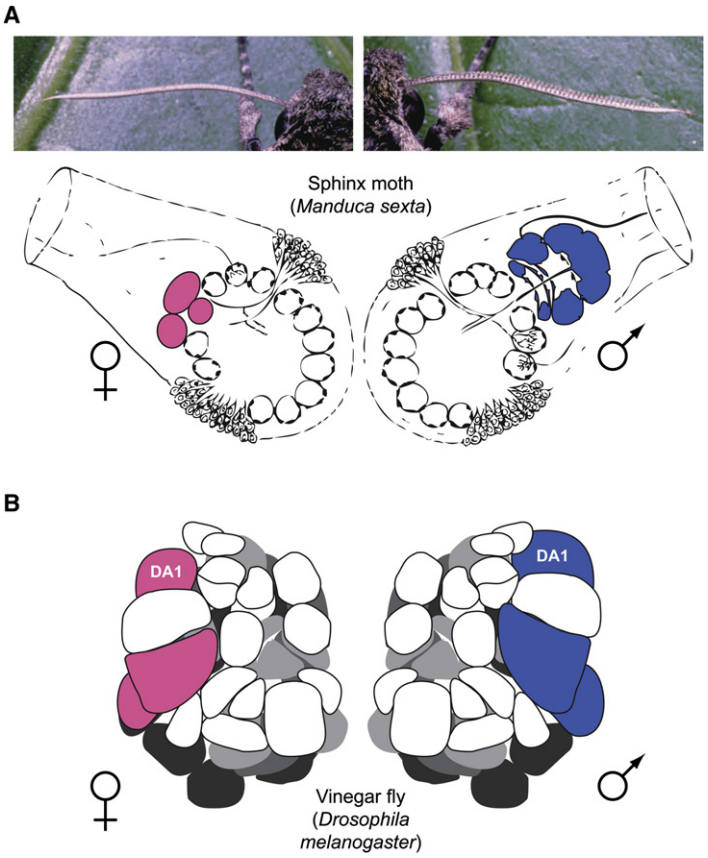

Figure 1. Sexual Dimorphism in Antennal Lobe Pheromone Circuitry Varies from Extreme to Subtle in Sphinx Moths and Vinegar Flies

(A) (Top) Images of the heads of female (left) and male (right) adult sphinx moths (*Manduca sexta*), illustrating the larger male antenna. (Bottom) Schematic of an antennal lobe of female (left) and male (right) adults, showing the sexually dimorphic glomeruli—the macroglomerular complex found only in the male (blue), and the three female-specific glomeruli (pink). Top image is copyright John Hildebrand, used with permission. Bottom image is adapted from the Summer Bulletin of the American Academy of Arts and Sciences, John Hildebrand, Bugs, Behavior, and Biomolecules: The Naturalist's Guide to the Future. Pt. 3: Neural Processing, 26–31, copyright 2004, with permission from John Hildebrand.

(B) Female (left) and male (right) antennal lobes from the vinegar fly (*Drosophila melanogaster*) are only subtly sexually dimorphic. Glomeruli innervated by *fru*+ neurons (Manoli et al., 2005; Stockinger et al., 2005) are indicated in pink in the female and in blue in the male. These glomeruli are present in flies of both sexes but are significantly larger in the male. The cVA-sensitive glomerulus, DA1, is indicated. Antennal lobe sections are presented from anterior to posterior, with depth-coding of black for posterior, gray for intermediate, and white for anterior sections. Adapted from Curr. Biol. 15, Fishilevich and Vosshall, Genetic and functional subdivision of the *Drosophila* antennal lobe, 1548–1553, copyright 2005, with permission from Elsevier.

postsynaptic to Or67d sensory neurons are selectively tuned to cVA, suggesting that this represents a labeled line circuit (Schlief and Wilson, 2007).

Or67d mutants lack electrophysiological responses to cVA and mutant flies show behavioral problems: mutant males developed by Barry Dickson's group court other males, while mutant females are less sexually receptive (Kurtovic et al., 2007). Intriguingly, Leslie Griffith, John Carlson, and coworkers identified a second cVA receptor, *Or65a*, in their studies (Ejima et al., 2007; van der Goes van Naters and Carlson, 2007). The ligand tuning of Or65a is slightly less specific and responses to cVA are weaker than those of Or67d, but behavioral experiments implicate Or65a and not Or67d as the receptor relevant for suppressing courtship of previously mated females. The basis for this discrepancy is currently not known, but both groups used different genetic approaches and measured different behaviors. The availability of Or65a mutant flies would help to resolve this conflict. Whether Or65a or Or67d (or both) mediates the behavioral effects of cVA, both receptors are present in males and females. Therefore, the mechanism for the dimorphism in response to this male pheromone must lie elsewhere.

A Surprising Coreceptor Plays in the cVA Detection Game

Although genetic evidence strongly supports the notion that Or67d is a major receptor for cVA, recent work from my group and Dean Smith's suggests that insect pheromone receptors do not act alone. Forward and reverse genetic experiments showed that an insect-specific CD36 homolog called Sensory Neuron Membrane Protein (SNMP), originally identified in the moth (Rogers et al., 1997), is a coreceptor for cVA (Benton et al., 2007; Jin et al., 2008) (Figure 2). This small two-transmembrane-domain protein is selectively expressed in olfactory neurons that detect pheromones, is in proximity to the Or67d+Or83b complex in the membrane, and when mutated, increases the spontaneous activity of these neurons and renders them insensitive to cVA. SNMP appears to facilitate pheromone action, but not govern ligand specificity. This conclusion is based on experiments in which we exchanged the Or67d cVA receptor for a moth receptor and changed the tuning profile of the sensory neuron from cVA to the moth pheromone (Benton et al., 2007).

LUSH: Binding Protein, Ligand, or Both?

How does the large hydrocarbon cVA molecule access the Or67d+Or83b+SNMP receptor complex in the membrane? An intriguing answer seems to lie in a small secreted member of the olfactory binding protein superfamily call LUSH or OBP76a. LUSH is both required for sensitive cVA detection and for modulating the spontaneous activity of Or67d-expressing sensory neurons (Xu et al., 2005; Ha and Smith, 2006) (Figure 2). Based on these results, Dean Smith's group postulated that LUSH is more than a soluble carrier protein that simply delivers cVA to the pheromone receptor. In fact, a recent structural biology paper from Smith and David Jones's group strongly suggests that LUSH itself may be the ligand for the pheromone receptor (Laughlin et al., 2008). When LUSH binds cVA, it undergoes a pheromone-dependent structural change. A LUSH point mutation that mimics this cVA-induced conformational change yields a dominant variant that activates neurons in the absence of pheromone (Laughlin et al., 2008).

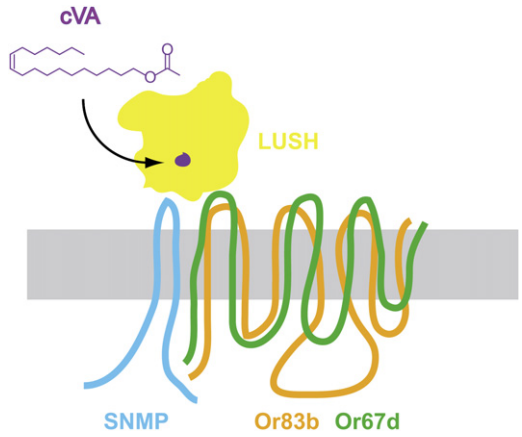

Figure 2. The Pheromone cVA Is Sensed by a Multisubunit Receptor Complex

Schematic drawing of cVA signaling, which begins when cVA (purple) is bound to LUSH (yellow), changing its conformational state. Pheromone-bound LUSH then interacts with the receptor complex comprising the CD36 homolog, SNMP (cyan), and the insect odorant receptor complex of Or67d (green) and Or83b (orange). The relative stoichiometry and details of cVA+LUSH interaction with SNMP+Or67d+Or83b remain to be elucidated.

This exciting work supports a model in which LUSH becomes a specific protein ligand for the Or67d+Or83b+SNMP complex only after binding cVA, and in which the pheromone-induced conformer of LUSH, and not the pheromone per se, constitutes the active ligand for Or67d (Laughlin et al., 2008). This conclusion is reminiscent of that reached in a recent paper from Lisa Stowers, whose group showed that mouse urinary proteins (MUPs) activate pheromone-sensitive mouse vomeronasal neurons independent of small molecule ligands (Chamero et al., 2007).

The precise biochemical details of how the pheromone cVA interacts with LUSH and the three membrane-bound receptors of Or67d+Or83b+SNMP remain to be elucidated (Figure 2). van der Goes van Naters and Carlson (2007) found that weak pheromone-evoked responses can be elicited when cVA is physically applied to neurons expressing Or67d+Or83b ectopically without the SNMP coreceptor and without LUSH (van der Goes van Naters and Carlson, 2007). Working with a similar preparation, Dean Smith and my group found that high concentrations of cVA can activate Or67d-mediated responses in the absence of LUSH, but also that SNMP is required (Benton et al., 2007; Jin et al., 2008). In the native cVA-sensing neuron, both LUSH and SNMP are clearly required for pheromone detection. It will be fascinating to see if structural biology can provide insight into the inner workings of the multiprotein subunit insect pheromone receptor.

Sexual Dimorphism Begins in the Brain

None of the protein players involved in detecting cVA in peripheral sensory neurons appear to be expressed in a sexually dimorphic manner, suggesting that downstream neural processing encodes male- and female-specific responses to cVA. Unlike the extreme dimorphism in most moths, there is only limited sexual dimorphism on the *Drosophila* antenna. Males have slightly more pheromone-sensing trichoid sensilla, while females have slightly more food-sensing basiconic sensilla (Stocker, 1994). Similarly, there are no sex-specific glomeruli in *Drosophila* as there are in the sphinx moth (Figure 1). Instead, three glomeruli in the *Drosophila* antennal lobe (DA1, Va1l/m, and VL2a) are slightly but significantly larger in males than in females (Figure 1B) (Kondoh et al., 2003; Stockinger et al., 2005). One of these glomeruli, DA1, was shown to receive projections from olfactory neurons expressing Or67d, the cVA receptor (Kurtovic et al., 2007). These glomeruli are also the only three glomeruli that receive significant innervation from neurons expressing *fruitless* (*fru*), a putative zinc finger transcription factor that is a major regulator of male sexual behavior (Ito et al., 1996; Ryner et al., 1996; Manoli et al., 2005; Stockinger et al., 2005). When these *fru*-expressing neurons are silenced, anomalies in courtship behavior are observed (Manoli et al., 2005; Stockinger et al., 2005), further confirming that, while not as dimorphic as moth pheromone circuits, these neurons are tuned to pheromones.

Does the subtle sexual dimorphism in DA1 glomerulus size translate to any male-female differences in neural activation? To answer this question, various groups have begun to trace the connectivity of pheromone circuits to higher brain centers and also to investigate the physiological responses of second-order neurons to cVA. Second-order antennal lobe projection neurons elaborate dendrites that innervate specific glomeruli and then send axons to the mushroom body and the lateral horn of the protocerebrum. Liqun Luo and coworkers carried out a detailed analysis of the patterns of these projection neuron processes originating in different glomeruli. Interestingly, they reported both a clear segregation of pheromone and food sensing pathways to different broad domains of the lateral horn, and sexual dimorphism in innervation patterns within the pheromone domain (Jefferis et al., 2007).

To examine this putative dimorphism at a higher resolution, Richard Axel's group used an elegant GFP photoactivation technique (Datta et al., 2008) to label single *fru*+ projection neurons innervating the DA1 glomerulus. Electrophysiological analysis of these projection neurons demonstrated that they are activated by cVA equally in male and female brain (Datta et al., 2008). Thus, dimorphic male and female neural activation to cVA must occur at even higher synaptic levels. Indeed, careful reconstruction of the axonal termini of the cVA-sensitive projection neurons shows clear evidence of a male-specific branch in the lateral horn that depends on normal *fru* gene function. This suggests that third-order neurons may differ between males and females and that this higher-order dimorphism will ultimately explain the strongly dimorphic behaviors observed in response to cVA.

Sculpting a Male Brain with the *fru* Transcription Factor

The task of finding the central brain neurons that mediate sex-specific behaviors is an enormous one, but there has been much recent progress. The laboratories of Barry Dickson and Bruce Baker have each produced flies in which the male-specific variant of *fru* was expressed in females. This allowed both groups to demonstrate that *fru* is sufficient to induce male courtship behaviors in an otherwise female fly (Demir and Dickson, 2005; Manoli et al., 2005). This suggested that male-specific *fru* must somehow modulate the development, differentiation, or survival of a small group of male-specific neurons.

Shortly after the papers above were published, Daisuke Yamamoto and coworkers documented exactly this phenomenon: a small group of central brain neurons called mAL likely involved in taste sensation depends on *fru* function for survival, and these cells are programmed to die in normal females (Kimura et al., 2005). The same group has recently extended this work to demonstrate that another subset of male-specific neurons called the P1 neurons suffices to initiate female-directed courtship when masculinized in an otherwise female brain (Kimura et al., 2008). This group carried out painstaking experiments in which over 200 individual females with small patches of masculinized neurons generated with genetic mosaic techniques were tested for their latency to court normal females. Each female was then analyzed for the extent of masculinization in distinct *fru*-expressing neuronal clusters. In cases where the P1 cluster was masculinized, a high proportion of females showed spontaneous courtship toward other females. This paper represents an important step in assigning behavioral functions to individual *fru*-expressing neurons in the brain and extends previous efforts by Bruce Baker's group (Manoli and Baker, 2004).

How is neural output from a *fru*–dependent sexually dimorphic brain relayed to motor circuits? Gero Miesenböck's group used photoactivation of thoracic neurons that drive courtship song to demonstrate that, astoundingly, female flies have a latent courtship song circuit that can be revealed by genetic manipulation and removal of top-down cues (e.g., the head) (Clyne and Miesenbock, 2008). The quality of the courtship song, produced by unilateral vibration of either wing, in such headless flies (or "flyPods") depends on both the sex of the animal and male-specific *fru* expression. So while male and *fru*-expressing females produce a convincing courtship song that can stimulate sexual behavior of bystander flies that cannot produce their own song, normal female flyPods sing out of tune. This demonstration that normal females have an underlying motor program to produce a male-specific behavior is reminiscent of recent parallel discoveries in the mouse. Catherine Dulac's group showed that mutating the mTrpC2 ion channel, which lies downstream of pheromone receptors in the vomeronasal organ, uncovers female-directed copulation behaviors in female mice (Kimchi et al., 2007). Thus, in both flies and mice, sexuality is strongly influenced by pheromones, but the brain decides how the animal behaves.

Concluding Remarks and Future Outlook

Enormous progress has been made in understanding how the single male-specific compound cVA modulates sexual behavior in *Drosophila*. What excitement can we expect in the future in this area? We are missing the female side of the fly courtship story. Although long inferred from behavioral studies, a pheromone that broadcasts virginity has not yet been identified or characterized. It will be fascinating to study how this putative molecule is detected by males and how central circuitry allows males to distinguish between a virgin and a recently mated nonvirgin, who will send mixed messages of virginity and the acquired maleness of cVA. Chemical cues that allow a *Drosophila melanogaster* male to distinguish females of his own species from that of closely related *Drosophila* species is another important unexplored area. Finally, the circuit-level details of how pheromones initiate highly stereotyped male and female sexual behaviors are only beginning to be understood. Thus, almost a century of *Drosophila* geneticists peeping in on the sex lives of flies has provided important insights into the signaling and circuits that control sexual behavior.

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