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Current Opinion in Neurobiology

Mating pheromones of *Nematoda*: olfactory signaling with physiological consequences

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Secreted pheromones have long been known to influence mating in the phylum *Nematoda*. The study of nematode sexual behavior has greatly benefited in the last decade from the genetic and neurobiological tools available for the model nematode *Caenorhabditis elegans*, as well as from the chemical identification of many pheromones secreted by this species. The discovery that nematodes can influence one another's physiological development and stress responsiveness through the sharing of pheromones, in addition to simply triggering sexual attraction, is particularly striking. Here we review recent research on nematode mating pheromones, which has been conducted predominantly on *C. elegans*, but there are beginning to be parallel studies in other species.

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Current Opinion in Neurobiology 2016, **38**:119–124

This review comes from a themed issue on **Neurobiology of sex**

Edited by **Barry J Dickson** and **Catherine Dulac**

For a complete overview see the Issue and the Editorial

Available online 21st May 2016

http://dx.doi.org/10.1016/j.conb.2016.04.008

Introduction

Nematoda is a diverse phylum of worms that occupy a variety of terrestrial, aquatic and marine habitats. Most nematode species are gonochoristic, consisting of males and females that must locate one another and mate to reproduce. Research on nematode mating pheromones began in the 1960s with an eye toward understanding the mating habits of animal-parasitic and plant-parasitic nematodes. Since then, it has been found that dozens of nematode species, most of them vision-impaired and hearing-impaired by nature, locate one another by the reception of secreted molecules (reviewed in [1]).

Most research on nematodes is conducted in the small, transparent *Caenorhabditis elegans*, which lives on rotting fruit and utilizes insect vectors as phoretic hosts. This nematode, unlike most, is androdiecious in nature, consisting of self-fertilizing hermaphrodites and rare males (reviewed in [2]). The hermaphrodites are incapable of mating with one another, and may only self-fertilize using a limited supply of self-sperm generated during larval development — reproduction after the exhaustion of self-sperm can only proceed by mating with a male. That mating is strictly unnecessary for survival of *C. elegans* makes this species an excellent model for the study of mating behavior [3], as the mating process can be disrupted at nearly every step without sacrificing the organism's viability [4].

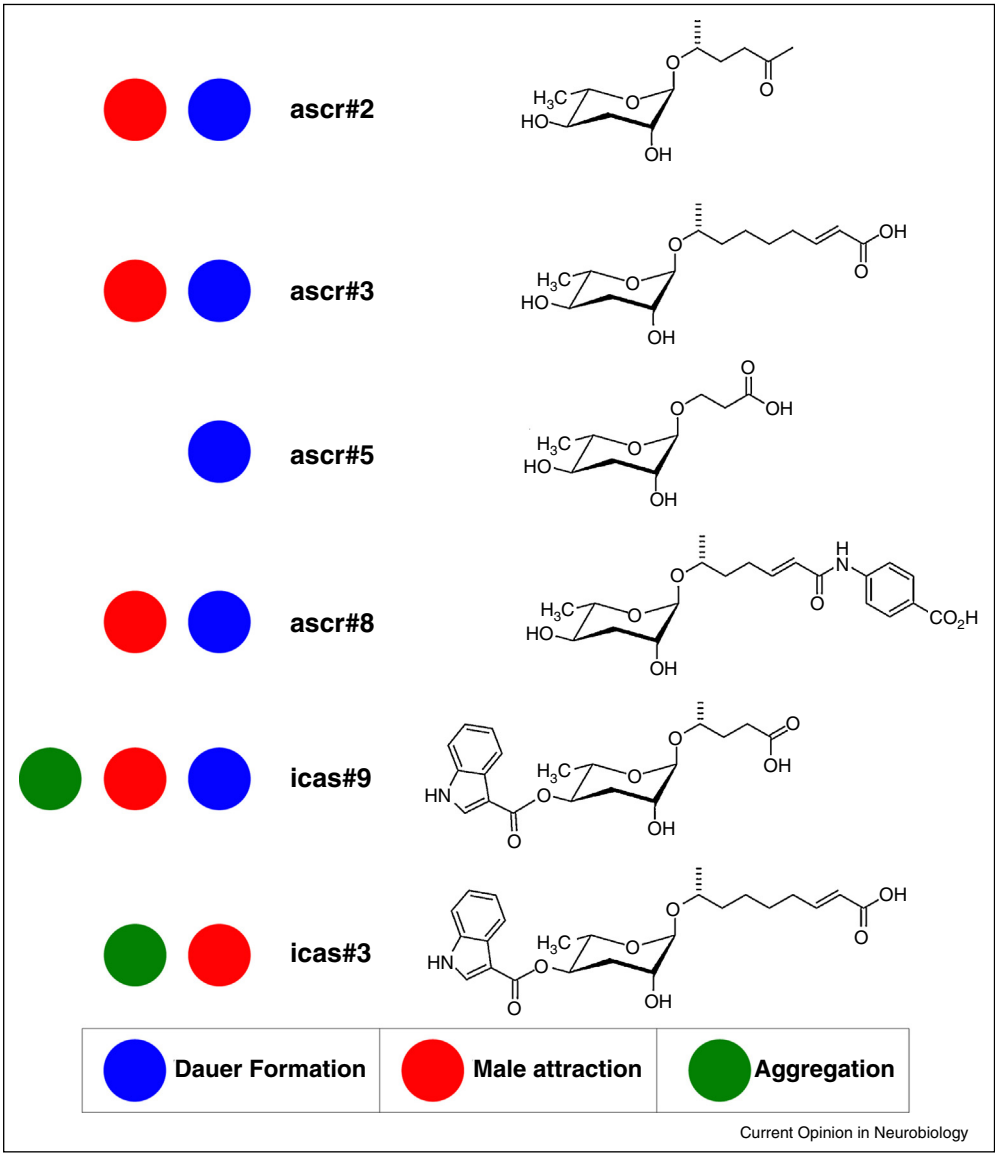
The discovery that many disparate species utilize ascarosides, a nematode-specific family of glycolipids, for communication, has greatly accelerated the rate of research in this field (reviewed in [5]). The research reviewed here largely took advantage of the ability to identify specific pheromones and challenge worms with pure synthetic compounds to uncover the precise neurological and physiological activities of these molecules.

Ascarosides

The ascarosides are glycosides of the dideoxysugar ascarylose. These molecules always include a lipid tail, and may be conjugated to amino acid derivatives or other small molecules [6]. Ascarosides are now known to be produced by over twenty species of nematode from multiple clades, including free-living, vertebrate parasitic and insect parasitic worms [7]. Ascarosides have been demonstrated as mate-attracting pheromones both *C. elegans* [8] and *Panagrellus redivivus* [9], despite these species' significant evolutionary distance, lying in different families. Ascarosides have also been shown to promote entrance into dauer, an alternative non-feeding and stress resistant larval stage, in *C. elegans* [10a], *Heterorhabditis bacteriophora* [11] and *Pristionchus pacificus* [12]. As would be expected of signaling molecules, ascaroside production varies with a worm's age and environment [13]. In both *C. elegans* and *P. redivivus*, the different genders secrete specific ascarosides in vastly different quantities, with each gender producing the attractants for the other. In addition, the *C. elegans* hermaphrodite secreted pheromones are repulsive to other hermaphrodites [9,14]. Taken together, this evidence suggests that ascarosides are evolutionarily ancient signaling molecules that may serve as mating pheromones across much of *Nematoda*.

In addition to being a highly diverse molecular family with over 150 members, the specific activity of each ascaroside is highly dependent on its chemical structure

Figure 1



The behavioral response of *Caenorhabditis elegans* to specific ascarosides is highly dependent on chemical structure.

[15] (Figure 1), and the same ascaroside can have extremely different effects on different species. For example, ascr#1 is a potent mate-attracting pheromone in *P. redivivus*, but promotes dauer formation in *C. elegans* [9,10a,16]. In fact, evolution of ascaroside signaling appears to be extremely rapid even within a species. The production and reception of dauer pheromones by both *C. elegans* and *P. pacificus* differs markedly amongst wild isolates of both species, possibly as a result of intense intraspecific competition over food resources [12,17••]. Different strains of the same nematode are even known to mate at different rates, though this may have both pheromone-related and other reasons [18]. Ascarosides are also known to trigger feeding behavior in nematophagous fungi [19], and immune reactions in plant hosts [20••], which likely apply additional pressure on the rapid evolution of nematode pheromones. Additionally, the ability of a nematode to locate a mate depends on more than simply chemotaxis to a pheromone cocktail. For example, Sammut *et al.* (2015) have recently shown that *C. elegans* males can be conditioned to associate a particular salt concentration with potential mates [21].

The essentially invariant anatomy of *C. elegans*, coupled with the ability to identify specific neurons under Nomarksi microscopy, has allowed researchers to identify