DISPATCH

Animal behaviour: Shifting attention in order to disperse

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New findings in the nematode *Caenorhabditis elegans* identify neuromodulation of behavioural responses to pheromones as a mechanism for regulating dispersal and foraging strategies.

Dispersal as a foraging strategy (i.e. the search for new sources of food) is a behaviour critical for survival. Foraging in a constantly changing environment requires integration of information about food availability as well as social cues, such as pheromones, which signal the presence of potential competitors. The bacterivorous nematode *Caenorhabditis elegans* is a powerful system to study how the integration of food and pheromone signals shape foraging behaviour. *C. elegans* has a 'boom and bust' life cycle in which food availability and population density change rapidly and dramatically[1]. Therefore, worms need to collect and integrate information about these variables to decide whether to exploit a given environment or explore in search of a new one. Several factors have been shown to modulate *C. elegans* foraging and dispersal. These include food abundance[2,3] food nutritional value[4], population density[3] (which is sensed through blends of pheromones called ascarosides[5]), experience[6] and biological sex. However, the neural mechanisms by which all these signals are integrated to modulate foraging remain poorly understood. In this issue of *Current Biology*, Luo and Portman[7] provide new insight into the molecular and cellular regulation of foraging in a sexually dimorphic context.

By systematically changing the thickness of the bacterial lawn on which *C. elegans* feed, these authors find that responses to the pheromone ascr#3, which signals population density, are modulated by food abundance and in a sex-specific manner. Hermaphrodites chronically avoid ascr#3, but avoidance is reduced when food is abundant. Males, instead, are attracted to ascr#3[8] and this response is independent of food abundance. Luo and Portman[7] also show that integration of food signals and pheromones in hermaphrodites requires signalling by the neuropeptide pigment-dispersing factor (PDF). Mutant hermaphrodites lacking the PDF receptor PDFR-1 avoid ascr#3 even when plenty of food is available. Conversely, increasing PDFR-1 signalling, by ligand overexpression, reduces ascr#3 avoidance when food is limited[7]. Therefore, the intensity of PDFR-1 signalling, mainly in a PDF-1-dependent manner, could encode information about food abundance to modulate ascr#3 avoidance.

Where does PDFR-1 act to modulate ascr#3 avoidance? To answer this question, the authors used a previously described intersectional genetic strategy to restore PDFR-1 signalling in a cell-specific manner[9]. They show that PDFR-1 is required in the nervous

system, specifically in a small group of interneurons (AIA, PVC, AVA, AVD, AVE, AVG and RIM), likely by modulating the processing and perception of the pheromone signal rather than its sensation.

Next, the authors go on to investigate the neural substrates for ascr#3 detection. Ascr#3 is not only a population density marker but also a sex pheromone and, as mentioned earlier, males and hermaphrodites display very different responses to ascr#3: males show attraction, whereas hermaphrodites show repulsion[8,10,11]. Such dimorphism may be explained by the need to incorporate reproduction demands into behavioural decisions. For self-fertilising hermaphrodites, whose reproductive priority is to find a suitable environment to lay eggs, high levels of pheromones indicate competition for resources. In contrast, for males, whose reproductive priority is to find a mating partner, pheromones indicate a potential source of mating opportunities.

The circuits mediating responses to ascr#3 are also sexually dimorphic. Previous studies showed that acute responses to ascr#3 in the absence of food require the ADL and ASK neurons in hermaphrodites and the ASK and CEM neurons in males[8,10,11]. However, combining genetic ablation of neurons and behavioural analysis, Luo and Portman[7] find that chronic avoidance of ascr#3 in hermaphrodites requires a different class of neurons, the ASI neurons. Regarding males, the Portman lab has previously shown that chronic attraction to ascr#3 is mediated by ADF neurons[12]. In the present work, these authors further show that removing ASI function in males does not disrupt attraction to ascr#3. However, if ADF is removed in males, they now display repulsion to ascr#3, like hermaphrodites, and this is also mediated by ASI. Therefore, in males there is a latent circuit that mediates hermaphrodite-like responses to pheromones. Interestingly, a latent circuit driving pheromone-dependent male-specific sexual behaviour has also been found in female mice[13]. A further interesting observation is that, although PDF signalling dampens ascr#3 avoidance in both hermaphrodites and ADF-ablated males, modulation of ascr#3 avoidance by food occurs only in hermaphrodites and not in males. This suggests that PDF signalling in males may be encoding something other than food abundance.

The TGFβ superfamily ligand DAF-7 is one of the modulators secreted by ASI, and, similarly to ASI-ablated animals, *daf-7* mutant hermaphrodites exhibited no response to ascr#3 regardless of food thickness[7]. This suggests that DAF-7 may mediate the ASI-driven avoidance of ascr#3. Since previous studies have shown that pheromones as well as a scarcity of food downregulate the expression of DAF-7[14], the studies of Luo and Portman[7] suggest that low levels of DAF-7 may mediate dispersal away from a thin lawn of food also containing pheromone. This is somewhat in contrast to other work, which has shown that foraging and dispersal require high levels of DAF-7[2]. Further work is needed to reconcile these findings; determination of when exactly DAF-7 is required to mediate dispersal in these different contexts may help. One possibility is that DAF-7 may play different roles during development and during adulthood to regulate pheromone sensing and foraging. Indeed, functional ASI neurons and DAF-7 signalling are necessary during development in males so that proper pheromone responses are elicited during adulthood[15].

One open question remaining from the work by Luo and Portman[7] is what exactly does PDF signalling encode? The authors propose that PDF encodes information about food.

This information may be relayed through mechanosensation of bacteria by ADE or detection of metabolic gases via RMG (both of these neurons express PDF-1)[16]. However, recent findings provide an alternative interpretation: Dal Bello *et al.*[17] show that worms change their preference for pheromones from attraction to repulsion when food is scarce, and this switch in preferences is due to associative learning between pheromones and food. Therefore, PDF-mediated dampening of ascr#3 aversion in thick food lawns may be a consequence of learning and integration of pheromones with food. Indeed, a role for PDF-1 in mediating associative learning of salt with pheromones has been reported in males[18]. Furthermore, Luo and Portman[7] show that PDF signalling modulates ascr#3 by acting on AIA, a class of interneurons previously shown to underlie the aversive associative learning of attractive stimuli with lack of food[19]. Another potential function of PDF proposed by Luo and Portman[7] is the modulation of attention to sensory stimuli. We agree with this interpretation and would like to extend it by proposing that PDF may function to shift attention away from one salient stimulus towards another to reorganise the hierarchy of behavioural priorities. This proposed function for PDF is consistent with the findings of several previous studies reviewed in Flavell *et al.*[20] as well as with the current work by Luo and Portman[7]. When food is abundant, it may be adaptive for hermaphrodites to ignore population density (through PDF modulation) and instead exploit an enriched environment. However, when food is being depleted, pheromones may be more salient because population density indicates competition for resources. This model is tested by Luo and Portman[7] with an elegant experiment in which they measure the dispersal rates from food patches of different thickness (scarce or abundant) in the presence or absence of ascr#3. Indeed, they find that dispersal rates are highest when food is low and pheromone is high and that this requires ASI neurons.

Taken together, the work of Luo and Portman[7] identifies sexually dimorphic neurogenetic mechanisms underlying the integration of food and social cues during foraging. The findings also open new and interesting questions about the role of neuromodulators and the underpinnings of their sexually dimorphic influence.

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Figure 1. Sexually dimorphic responses to the pheromone ascr#3 result in different foraging strategies.

(A) Behavioural avoidance response of *C. elegans* hermaphrodites to the pheromone ascr#3 as well as its cellular (ASI neuron) and molecular (DAF-7) regulators. The left panel indicates

a dampening of the avoidance response through PDF-1 modulation and according to food abundance, reducing dispersal from a food-rich environment. (B) Attractive behavioural response of *C. elegans* males to the pheromone ascr#3 (mediated by the ADF neuron); this response is not modified by food availability.