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A dual mechanosensory and chemosensory neuron in *Caenorhabditis elegans*

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ABSTRACT **After light touch to its nose, the nematode *Caenorhabditis elegans* halts forward locomotion and initiates backing. Here we show that three classes of neurons (ASH, FLP, and OLQ) sense touch to the nose and hence are required for this avoidance response. ASH, FLP, and OLQ have sensory endings that contain axonemal cilia. Mutant animals that have defective ciliated sensory endings as well as laser-operated animals that lack ASH, FLP, and OLQ fail to respond to touch to the nose. Together with the previous work of others, these results demonstrate that *C. elegans* has at least five morphologically distinct classes of mechanosensory neurons. Interestingly, the ASH neuron also acts as a chemosensory neuron; it mediates the avoidance of noxious chemicals. Since ASH possesses both chemosensory and mechanosensory modalities, this neuron might be functionally analogous to vertebrate nociceptors, which mediate the sensation of pain.**

Animals are exquisitely sensitive to a wide variety of mechanical stimuli, which are sensed by many distinct classes of mechanosensory neurons. For example, in mammals, the vestibular cells of the ear sense gravity (1), muscle receptors sense limb position and movement (2), and five classes of neurons sense cutaneous mechanical stimuli (3). Each class of mechanosensory neuron is morphologically distinct and can be distinguished histologically. Each class typically responds to a single type of mechanical stimulus and hence corresponds to a distinct sensory modality (e.g., sense of equilibrium, sense of spatial position, and sense of touch). However, some neurons (polymodal neurons) are sensitive to multiple types of stimuli. For example, a class of mammalian neurons that sense painful stimuli (polymodal nociceptors) responds to thermal, chemical, and mechanical stimuli (4).

One class of *Caenorhabditis elegans* mechanosensory neurons has been extensively characterized (5–7). The neurons ALM, AVM, PLM, and PVM (Fig. 1) have sensory endings that contain 15-protofilament microtubules rather than the 11-protofilament microtubules found in most *C. elegans* neurons (10) and hence are called the microtubule touch cells. These neurons sense touch; they divide the worm's body into two apparent sensory fields, anterior and posterior. Mutations in 20 genes disrupt either the development or function of the microtubule touch cells (7).

We report here our characterization of an additional mechanosensory reflex, avoidance of touch to the worm's nose. Light touch to the nose causes worms to halt forward locomotion and initiate backing. We found that normal animals responded to this stimulus in 90% of the trials (Table 1, row 1). Here we identify three additional classes of mechanosensory neurons (ASH, FLP, and OLQ) that mediate this avoidance response (Fig. 1), one of which (ASH) is a polymodal sensory neuron.

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MATERIALS AND METHODS

Neuron Designations. Classes of neurons are designated as described by White *et al.* (9). Briefly, neuronal classes in *C. elegans* are defined on the basis of similarities in axonal morphologies and synaptic connectivities. The members of each class differ in only their anatomical positions. For example, there are two ASH neurons, one on the left (ASHL) and one on the right (ASHR) side of the animal. If positional descriptors (L and R for left and right; D and V for dorsal and ventral) are not indicated, then the name refers to all members of a class.

Laser Microsurgery and Culture. In general, neurons were identified in first-stage (L1) larvae by the anatomical positions and the morphologies of their nuclei (14) and were killed by focusing a laser microbeam on identified nuclei by using the system described by Avery and Horvitz (15). The "All amphid" (Table 2, row 3) and "All but ASH" (Table 2, row 5) operations were performed on second-stage (L2) larvae, because killing some of these chemosensory neurons in L1 larvae causes the animals to develop into dauer larvae instead of adults (17). In all cases, all members of the indicated class of neurons were killed in these experiments. Some amphid neurons (ADF, ADL, ASH, ASI, ASJ, and ASK) stain with the fluorescent dye 3,3'-dioctadecyloxacarbocyanine (18, 30). Laser-killing of these neurons was verified by staining animals with 3,3'-dioctadecyloxacarbocyanine and observing defects in the staining patterns. Combined ASH, FLP, and OLQ kills were verified in two laser-operated young adults (48 hr postoperatively) by examining electron micrographs of serial sections for the loss of ciliated sensory endings characteristic of these cells (J.M.K., E. Hartwieg, and H.R.H., unpublished observations). Avoidance responses were examined 48 hr postoperatively, when animals were generally young adults. Nematodes were grown under standard conditions on lawns of the auxotrophic *Escherichia coli* strain OP50 (19).

Analysis of Touch Avoidance. Body regions are defined as follows: the nose is the anterior-most tip of the animal, the anterior body region lies between the posterior bulb of the pharynx and the vulva, and the posterior body region lies between the vulva and the tail.

The response to touching the nose was tested by placing an eyelash in the path of an animal moving forward, causing a "nose-on" collision. The response to touching the anterior body region was tested by stroking an animal with an eyelash at the posterior bulb of the pharynx, as described (5, 6). In both cases, a trial was scored as a success when animals either halted forward locomotion or initiated backward movement following the stimulus.

Individual experimental animals—together with equal numbers of positive (unoperated wild-type animals) and negative (cilia-defective mutants) controls—were assayed as young adults by an experimenter unaware of their genotype

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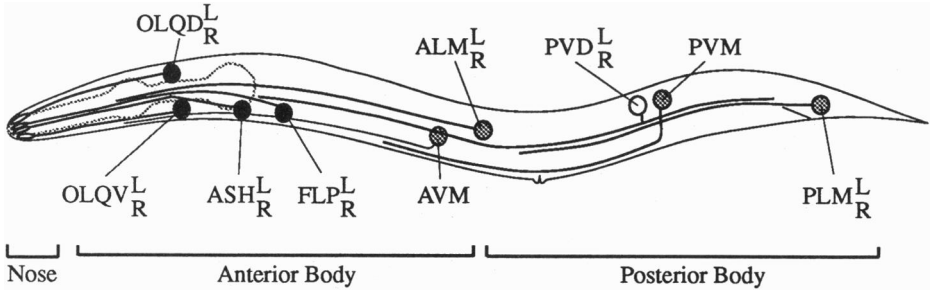

FIG. 1. The somatosensory system of *C. elegans* consists of five classes of mechanosensory neurons. Three (black circles) have ciliated sensory endings (represented as ovals) at the tip of the nose; another class, the microtubule touch cells (gray circles), has sensory endings that contain 15-protofilament microtubules; and the third class (white circle) has undifferentiated sensory endings. The ASH, FLP, and OLQ neurons sense touch to the nose. The microtubule touch cells (ALM, AVM, PLM, and PVM) sense touch along the entire length of their dendrites. AVM and the ALM neurons sense touch to the anterior body region, whereas the PLM neurons sense touch to the posterior body region (5, 6). Although no behavioral function has been ascribed to the PVM neuron, it might also sense touch to the posterior body region. The PVD neurons sense only very intense mechanical stimuli (8). The anatomical descriptors used are left (L), right (R), dorsal (D), and ventral (V). For example, OLQDR is the dorsal OLQ neuron on the right side. The positions of neuronal nuclei and sensory endings are as described (9). This figure illustrates the left lateral side of the worm.

and operative status (exceptions are indicated). Each animal was usually subjected to 50 total trials, administered in five sets of 10 consecutive trials. The number of successes in each set of 10 trials was recorded as a single data point. Between sets of 10 trials, animals were given a rest of at least 10 min. Habituation to the stimulus was not observed using this paradigm.

Statistical Methods. All statistical analyses were performed using SAS software (20).

The behavior of groups of animals (a group defined by either genotype or operative status) was compared by ANOVA (21). The Tukey test was used to control for multiple comparisons (21). Comparisons that were statistically significant ($P < 0.01$) are indicated by "Yes" in Tables 1 and 2 or are indicated in the text. We found no statistical differences between animals within a group (data not shown).

Avoidance of touch to the nose by laser-operated animals was also analyzed by multiple linear regression (21), according to the following model: avoidance = $\beta_0 + \beta_1$ASH + β_2FLP + β_3OLQ. When a neuron was killed, the value for that variable was set to zero. The data for this analysis were derived from Table 2, rows 1, 4, 7, 8, 9, 11, 12, and 13. Coefficients for ASH (β_1), FLP (β_2), and OLQ (β_3) derived from this analysis are indicated. The probability that each of these coefficients is different from zero (P) was determined by comparison to a T distribution.

RESULTS AND DISCUSSION

We pursued two strategies to identify the neurons that sense touch to the worm's nose. First, we analyzed the behavior of mutant animals with ultrastructural defects in sensory neurons; such mutants were previously isolated in genetic screens for animals with defective mechanosensory (5, 6) or chemosensory responses (11–13). Second, we killed identified neurons with a laser microbeam and tested the touch sensitivities of the laser-operated animals. Such laser experiments are possible because *C. elegans* has a simple nervous system, consisting of only 302 neurons in the adult. These 302 neurons comprise 118 anatomically defined classes, and equivalent neurons in different animals have very similar anatomical positions, axonal morphologies, and synaptic connectivities (9, 22–24). The relative invariance of the animal's neuroanatomy coupled with the ability to kill identified neurons with a laser microbeam (5, 6, 16) has made it possible to study *C. elegans* behavior at the resolution of single cells (5, 6, 8, 15–17, 25).

Microtubule Touch Cells Do Not Sense Touch to the Nose. Previous studies by Chalfie and coworkers (5, 6) established that the microtubule touch cells ALM and AVM sense touch to the anterior body region (Fig. 1). These authors also showed that *mec*hanosensory-defective mutants that have ultrastructurally and functionally defective microtubule touch cells (for example, *mec-4* and *mec-7* animals) respond

Table 1. Cilia-defective mutants fail to avoid touch to the nose

Genotype	Cilia affected*	Avoidance, % responding	95% confidence interval, %	No. animals (no. trials)	Different from wild type ($P < 0.01$)
1. N2 (wild type)	None	90	89–91	106 (5060)	—
2. *che-2(e1033)*	All	46	38–54	10 (500)	Yes
3. *che-3(e1124)*	All	9	6–12	10 (500)	Yes
4. *che-13(e1805)*	All	19	13–25	11 (520)	Yes
5. *osm-6(p811)*	All	30	23–42	12 (510)	Yes
6. *che-12(e1812)*	Amphid and phasmid	71	64–78	11 (440)	Yes
7. *osm-3(p802)*	Amphid and phasmid	51	45–57	11 (550)	Yes
8. *che-5(e1073)*	NA	91	87–95	10 (520)	No
9. *che-7(e1128)*	None	91	87–95	13 (620)	No

Avoidance of touch to the nose by individual animals was determined as described in *Materials and Methods*. The following cilia-defective strains were also examined: *che-10(e1809)*, *che-11(e1810)*, *daf-10(e1387)*, *daf-19(m86)*, *osm-1(p808)*, and *osm-5(p813)*. All of these strains were defective for the avoidance response following light touch to the nose. These data were not included in the table because some of the animals were not scored in blind tests. Genotypes are indicated by the name of the gene (e.g., *che-2*) followed by the name of the specific allele tested (e.g., *e1033*) (31). NA, not analyzed.
*Ultrastructural defects in the ciliated sensory endings of these strains are indicated, as previously reported: rows 2, 3, and 9 (11); row 3 (12); rows 4–7 (13).

Table 2. ASH and FLP mediate avoidance of touch to the nose

Neuron classes killed*	Avoidance, % responding	95% confidence interval, %	No. animals (no. trials)	Different from unoperated controls ($P < 0.01$)
1. None	90	89–91	106 (5060)	—
Microtubule touch cell				
2. ALM + AVM†	84	79–89	10 (500)	No
Amphid				
3. All amphid‡	46	35–56	4 (190)	Yes
4. ASH	35	27–44	8 (400)	Yes
5. All but ASH§	96	94–98	6 (300)	No
6. All ASH inputs¶	94	91–97	5 (250)	No
Nonamphid				
7. FLP‖	63	57–70	9 (460)	Yes
8. OLQ	84	78–90	9 (450)	No
9. FLP + OLQ**	48	41–56	9 (450)	Yes
10. All but FLP and OLQ††	95	93–98	5 (250)	No
Combinations				
11. ASH + FLP**	17	11–24	9 (450)	Yes
12. ASH + OLQ	46	38–54	8 (400)	Yes
13. ASH + FLP + OLQ‖‡‡	10	5–15	11 (530)	Yes

Avoidance of touch to the nose by individual laser-operated animals was determined as described in *Materials and Methods*.

*Neuron designations are as described (9). In all cases, all members of the indicated class of neurons were killed.

†The precursor to AVM, QR (16), was killed in combination with the two ALM neurons.

‡All amphid sensory cells (i.e., ADF, ADL, AFD, ASE, ASG, ASH, ASI, ASJ, ASK, AWA, AWB, and AWC).

§All amphid neurons except ASH (i.e., ADF, ADL, AFD, ASE, ASG, ASI, ASJ, ASK, AWA, AWB, and AWC).

¶All neurons that provide synaptic input to ASH (i.e., ADA, ADL, AIZ, ASI, ASK, HSN, RIF, RIC, and RMG) (9).

‖These animals were not scored blind.

**Animals lacking both of these neurons differed significantly ($P < 0.01$) from those lacking either alone.

††The five classes of nonamphid neurons, other than FLP and OLQ, that have ciliated sensory endings in the nose (i.e., BAG, CEP, IL1, IL2, and OLL).

‡‡The responses of these animals did not differ significantly from those of animals lacking only ASH and FLP (row 11).

to touch to the nose. We have confirmed these observations (data not shown). To test directly whether ALM and AVM sense touch to the nose, we killed these neurons with a laser microbeam. We found, as previously reported (5, 6), that animals lacking ALM and AVM no longer responded to touch to the anterior body region but still responded to touch to the nose (Table 2, row 2). These results indicate that ALM and AVM are not necessary for the animal to sense touch to its nose.

Cilia-Defective Mutants Fail to Respond to Touch to the Nose. What neurons might sense touch to the nose? Throughout the animal kingdom, many types of sensory neurons, including mammalian olfactory neurons and photoreceptors, have sensory endings that contain axonemal cilia. Nineteen classes of *C. elegans* neurons have ciliated endings in the nose (9, 11–13) and hence might sense touch to the nose. Thirteen of these classes are thought to be chemosensory because their ciliated endings are exposed to the external environment (9, 11–13) and because killing these neurons with a laser microbeam disrupts specific chemosensory behaviors (25, 26). These chemosensory endings are located in two sensory organs: the amphid (12 classes) and inner labial (1 class) sensilla. The remaining 6 classes are thought to be mechanosensory because their ciliated endings are not exposed to the external environment (9, 11–13).

To determine whether ciliated neurons sense touch to the nose, we examined the behavior of mutant animals that have defective ciliated sensory endings. Previous studies (11–13) demonstrated that several *che*motaxis (*che-2, che-3*, and *che-13*), *da*uer *f*ormation (*daf-10* and *daf-19*), and *osm*otic avoidance (*osm-1, osm-5*, and *osm-6*) defective mutants have severe ultrastructural defects in all ciliated sensory endings and that two mutants (*che-12* and *osm-3*) have defects in only the amphid and phasmid sensilla, the latter being a chemosensory organ in the worm's tail. We found that mutations in all of these genes significantly reduced ($P < 0.01$ in all cases) avoidance of touch to the nose (Table 1). By contrast, none of these mutations affected the response to touch to the body (13), presumably because the microtubule touch cells are not ciliated (10) and hence are not affected by these mutations. Chemotactic function *per se* is not required for avoidance of touch to the nose, since the chemotaxis-defective mutants *che-5* and *che-7* (Table 1, rows 8 and 9) responded to touch to the nose, and their behavior was indistinguishable from that of wild-type animals. These results suggest that ciliated neurons sense touch to the nose. Alternatively, the defects in the ciliated sensory endings might not cause the diminished touch sensitivity, if the mutants we studied also have defects in other, nonciliated neurons.

A Single Class of Amphid Neurons, ASH, Is Required for a Normal Response to Touch to the Nose. To confirm that defects in ciliated sensory neurons caused the impaired touch sensitivity of the cilia-defective mutants, we tested the effect of killing these neurons with a laser microbeam (Table 2). Because *che-12* and *osm-3* animals have defects in only the amphid and phasmid neurons (Table 1, rows 6 and 7) yet still have decreased touch sensitivity, we first tested the amphid neurons. (The phasmid neurons are unlikely to sense touch to the nose, because their sensory endings are in the tail.) Animals lacking all 12 classes of amphid neurons (Table 2, row 3) responded to touch to the nose in 46% of the trials, which differed significantly ($P < 0.01$) from the behavior of normal animals (Table 2, row 1). The defects in the amphid neurons of *che-12* and *osm-3* mutants are sufficient to explain the decreased touch sensitivity of these animals (Table 1, rows 6 and 7).

A single class of amphid neurons, ASH, is required for avoidance of touch to the nose. Preliminary experiments in which individual classes of amphid neurons were killed suggested that the ASH neurons are necessary for avoidance of touch to the nose (data not shown). When both ASH neurons were killed (Table 2, row 4), animals responded in

35% of the trials, which differed significantly ($P < 0.01$) from the behavior of normal animals (Table 2, row 1). No other amphid neurons are required for this behavior, because animals lacking all amphid neurons except ASH (Table 2, row 5) responded as well as unoperated controls. Inadvertant damage to cells adjacent to ASH is unlikely to explain these results, because all neurons that surround ASH were killed in the latter experiment with little effect. We conclude that ASH is the only class of amphid neuron required for avoidance of touch to the nose, accounting for roughly half of the normal response.

What Neurons Account for the Remainder of This Avoidance Response? Ciliated neurons outside the amphid probably also play a role, since mutants that have defects in all ciliated sensory endings [e.g., *che-3* and *che-13* (Table 1, rows 3 and 4)] were more defective than mutants that have defects in only the amphid and phasmid sensory endings [e.g., *che-12* and *osm-3* (rows 6 and 7)] and than laser-operated animals lacking only amphid neurons (Table 2, row 3). Thus, more extreme defects in touch sensitivity correlate with defects in both amphid and nonamphid ciliated sensory cells.

Chalfie and coworkers have predicted that the FLP neurons (Fig. 1) are mechanosensory because these neurons express the genes *mec-3* (8) and *mec-7* (32), which are required for the function and development of other mechanosensory neurons (7). To determine whether the FLP neurons mediate avoidance of touch to the nose, we killed these neurons with a laser microbeam. Animals lacking the FLP neurons responded in 63% of the trials (Table 2, row 7); animals lacking both the ASH and the FLP neurons responded in 17% of the trials (row 11). In both cases, the behavior of the laser-operated animals differed significantly ($P < 0.01$) from that of normal animals (Table 2, row 1). Furthermore, the behavior of animals lacking both ASH and FLP (Table 2, row 11) was significantly worse ($P < 0.01$) than that of animals lacking either ASH (Table 2, row 4) or FLP (Table 2, row 7).

One additional class of ciliated neurons (OLQ) appears to play a minor role in avoidance of touch to the nose. Animals lacking OLQ and FLP (Table 2, row 9) were slightly more defective ($P < 0.01$) than animals lacking only FLP (Table 2, row 7). We further assessed the importance of these neurons in this behavior by using a linear regression model (Table 3). This analysis indicated that ASH, FLP, and OLQ all contribute significantly to this avoidance response, with the order of importance being ASH > FLP > OLQ.

No other ciliated neurons are required for this avoidance response, because killing the remaining five classes of neurons that have ciliated sensory endings in the nose had no effect (Table 2, row 10). Thus, ASH, FLP, and OLQ are apparently the only ciliated neurons required for avoidance of touch to the nose.

Our laser experiments (Table 2) provide an explanation for the abnormal touch sensitivities of cilia-defective mutants (Table 1). First, the sensory ending defects of these mutants are sufficient to explain their decreased touch sensitivities, because the phenotypes of the most severe mutants, *che-3* and *che-13* (Table 1, rows 3 and 4), can be mimicked by killing ASH, FLP, and OLQ (Table 2, row 13). Second, differences in the sensory ending defects can account for some of the quantitative differences in touch sensitivity among mutants. Mutants that are less sensitive to touch [e.g., *che-3* and *che-13* (Table 1, rows 3 and 4)] have defects in all sensory endings, whereas those that are more sensitive to touch [e.g., *che-12* and *osm-3* (Table 1, rows 6 and 7)] have defects in only the amphid and phasmid sensory endings (13). Differences among mutants that have defects in all ciliated sensory endings (Table 1, rows 2–5) correlate with differences in the severities of their ultrastructural defects. For example, *che-13* mutants, which have more severe ultrastructural defects than *osm-6* mutants (13), also have more severe defects in touch sensitivity (Table 1, rows 4 and 5). Thus, defects in ASH, FLP, and OLQ are sufficient to explain the touch sensitivities of the cilia-defective mutants.

Table 3. Linear regression model for avoidance of touch to the nose

Sensory cell	Coefficient	95% confidence interval	*P*
1. ASH	45	41–48	0.0001
2. FLP	29	26–33	0.0001
3. OLQ	5.1	1.7–8.5	0.0037

The contributions of ASH, FLP, and OLQ to avoidance of touch to the nose were estimated by multiple linear regression, as described in *Materials and Methods*. The fraction of the observed variance in the avoidance response explained by this model (*R*-square value) is 0.7.

Do ASH, FLP, and OLQ Act as Sensory Neurons in Touch Avoidance? The experiments we have described thus far do not distinguish whether these neurons act as mechanosensory neurons that directly sense touch, as interneurons that convey information from the true mechanosensory cells, or as accessory cells that provide some factor required for the function of the mechanosensory cells. Killing ASH, FLP, and OLQ would disrupt the avoidance behavior in all three cases.

We favor the model that ASH, FLP, and OLQ are themselves mechanosensory for two reasons. First, sensory endings are abnormal in the cilia-defective mutants (11–13), which suggests that ciliated neurons act as sensory neurons in this avoidance response. Second, ASH, FLP, and OLQ are uniquely required to respond to the stimulus. Killing all other ciliated neurons that have sensory endings in the nose had no detectable effect on this behavior. If ASH, FLP, and OLQ were acting as interneurons or as accessory neurons, then killing some other combination of sensory neurons (the true mechanosensory cells) would be predicted to disable touch avoidance.

We directly examined the role of ASH by killing all neurons that provide synaptic input to ASH. If ASH acts as an interneuron, then some of these neurons should also be required for avoidance of touch to the nose. When the nine classes of neurons that provide ultrastructurally identified synaptic inputs (electrical or chemical) to ASH (9) were killed (Table 2, row 6), animals responded as well as unoperated controls (Table 2, row 1). These results favor the hypothesis that ASH does not act as an interneuron in the neural circuit for this avoidance response.

Based upon all of our results, we propose that ASH, FLP, and OLQ directly sense touch to the nose.

Why Do Multiple Classes of Neurons Perform a Single Sensory Task? Our experiments identify three additional classes of mechanosensory neurons in *C. elegans*, all of which sense touch to the nose (Fig. 1). In *C. elegans*, multiple classes of neurons also sense touch to the body (refs. 5, 6, and 8; see Fig. 1) and particular chemical attractants (17, 26). Thus, as in vertebrates (27), in *C. elegans* multiple classes of neurons act in parallel to perform simple neural functions.

Devoting multiple neurons to sensing touch to the nose might be advantageous for several reasons. First, spatial information about mechanical stimuli could be encoded in this way. The sensory endings of ASHL/R and FLPL/R are in the left and right lateral labia of the nose, while those of OLQDL/R are in the two dorsal labia and those of OLQVL/R are in the two ventral labia (Fig. 1). Thus, in principle the worm could discriminate touch to six distinct sensory fields in the nose. We have shown that there must be at least two distinct sensory fields in the nose because worms have different responses to dorsal and ventral stimuli (J.M.K. and H.R.H., unpublished observations). Similarly, the mi-

crotubule touch cells (Fig. 1) could sense touch to six distinct body regions; however, there is behavioral evidence for only two sensory fields in the body, anterior and posterior (5).

A second advantage to having multiple neurons sense touch to the nose is that their combined function increases the overall sensitivity of *C. elegans* to this stimulus. When either the ASH neurons or the FLP neurons were killed (Table 2), animals responded to touch to the nose less often than did normal animals, indicating decreased sensitivity to touch.

Third, ASH, FLP, and OLQ could regulate distinct behaviors. Touch affects locomotion (refs. 5 and 6; this report), pharyngeal pumping (5, 6), defecation (28), foraging (unpublished observations), and egg-laying (B. Sawin and H.R.H., unpublished observations). We have found that the OLQ neurons control foraging behavior while ASH and FLP do not (unpublished observations), which suggests that individual mechanosensory cells regulate specific subsets of these behaviors.

Fourth, ASH, FLP, and OLQ might normally respond to subtly different stimuli. Five distinct classes of mechanosensory neurons contribute to cutaneous touch sensitivity in vertebrates, with each class responding to distinct stimulus intensities, stimulus frequencies, and receptive field sizes (3). Having cutaneous mechanosensors with various sensitivities allows an animal to discern a wide range of tactile stimuli. Similarly, some mechanosensory neurons in *C. elegans* also respond to distinct types of tactile stimuli. The microtubule touch cell AVM habituates to a train of stimuli more rapidly than does ALM (6), and the mechanosensory cell PVD responds to only very intense stimuli (8).

ASH Is a Dual Mechanosensory and Chemosensory Neuron. In addition to its role in touch avoidance, ASH also mediates avoidance of noxious chemicals, including hyperosmotic solutions and extracts of garlic (25). Thus, ASH is a multifunctional sensory neuron, responding to both mechanical and chemical stimuli. Perhaps chemosensory and mechanosensory information are integrated within this single sensory cell.

The ASH neuron might be functionally analogous to vertebrate nociceptors, which mediate the sensation of pain. Nociceptors are typically polymodal; some classes respond to both mechanical and chemical stimuli (4). Further, nociceptors are known to be chemically tuned (29). Injured tissues release chemical mediators of tissue inflammation (e.g., bradykinin, substance P, or hydrogen ions), which act directly on sensory endings, enhancing their sensitivity to mechanical stimuli (4, 29). Further investigation of the function of ASH might illuminate the mechanisms of pain sensation in vertebrates.

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