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Chemosensory organs as models of neuronal synapses

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Preface

Neuronal synapses are important microstructures that underlie complex cognitive capacities. Recent studies, primarily in *C. elegans* and *Drosophila*, have revealed surprising similarities between these synapses and 'sensory synapses' residing at the tips of chemosensory cells that respond to environmental stimuli. Similarities in the structure, mechanisms, and specific molecules found at these sites extend to the pre-synaptic, post-synaptic, and glial entities composing each synapse type. In this article I propose that chemosensory synapses may serve as useful models of neuronal synapses, and consider the possibility that both synapse types derive from a common ancestral structure.

Neuronal synapses, the physical structures connecting neurons to each other, are major sites of information processing in the nervous system. These synapses are composed of pre-synaptic and post-synaptic neuronal termini[1], and, in the case of excitatory synapses, are often ensheathed by glial extensions[2,3]. Information at neuronal synapses is conveyed by neurotransmitters released by presynaptic cells, and is processed at these sites by all three synapse-associated cells. Presynaptic neuronal termini control synaptic neurotransmitter activity by regulating release, reuptake, and neurotransmitter chemical structure. Postsynaptic termini control neurotransmitter efficacy by controlling recognition, through receptor choice, by inhibiting neurotransmitter activity (chemically or competitively), and by integrating multiple neurotransmitter signals from one or multiple presynaptic cells. Glial cells take up and release neurotransmitters, often in response to presynaptic neuronal cues, and also release neurotransmitter and neurotransmitter receptor inhibitors[4] (Box 1). The synapse is, therefore, a complex and highly regulated information processing module.

Sensory organs, like synapses, are also important sites of information processing. Environmental stimuli are encountered at these structures, and these signals are interpreted within sensory cells before passing on to higher levels of the nervous system. The dynamic range of sensory cells determines, in part, whether environmental signals can be distinguished from each other, and many sensory cells display adaptation aimed at blunting repetitive stimuli. Sensory capacities of modern day organisms are elaborate and diverse, and although it is unclear whether all sensory organs evolved from a common ancestral structure, some are likely to have evolved from a system whose primary task was the detection of environmental chemicals. Indeed, intriguing similarities between one class of animal and plant chemoreceptor and bacterial proteins tasked with detecting environmental chemicals[5-7] have been described, suggesting that chemosensation is a very ancient sensory modality.

Recent studies, primarily in the nematode *Caenorhabditis elegans* and the fruitfly *Drosophila melanogaster*, have revealed intriguing commonalities in the logic, organization, and molecular machineries used by chemosensory receptive structures and neuronal synapses. In each system, small molecules- either metabolites present in the environment or

neurotransmitters released by a presynaptic cell- bind to specific receptors localized to highly specialized cellular compartments on receptive neurons. Binding leads directly or indirectly to the opening or closing of ion channels, leading to neuronal activation or inhibition. Although receptor-ligand interactions occur widely in nature and control processes as diverse as cell-cell communication in the immune system, and endocrine signaling, the similarities uncovered in recent years between chemosensory organs and synapses go beyond generic parallels in signal transduction. Surprising molecular similarities have emerged between chemosensory structures and synapses at each level: the small molecule signals, the specialized receptive compartments, the identities of the receptors, and even the neighboring glia that surround each structure. These striking parallels suggest that 'chemosensory synapses' and perhaps 'sensory synapses' in general (not to be confused with the neuron-neuron synapses made by sensory neurons onto downstream interneurons) may be used to guide our understanding of neuron-neuron synapses. In this article, similarities between chemosensory receptive structures and neuron-neuron synapses are primarily explored, with additional parallels drawn from structures associated with other sensory modalities.

Presynaptic similarities

Although chemosensory-neuron termini are not associated with a physical presynaptic structure, there are parallels between the environmental food cues detected by chemosensory neurons, tuned to respond to essential food constituents, and presynaptically released neurotransmitters. For example, *C. elegans*, zebrafish, and mice can sense and chemotax towards amino acids, essential food constituents in their environment[8-10]. Likewise humans can taste amino acids (the Umami basic taste), and are particularly sensitive to the amino acid glutamate[11]. Many abundant and potent neurotransmitters are also amino acids[12]. These include glutamate, the major excitatory neurotransmitter in the mammalian brain, and glycine and GABA, two major inhibitory neurotransmitters. Other neurotransmitters, including serotonin, dopamine, epinephrine, norepinephrine, octopamine, and tyramine are derivatives of the amino acids tryptophan and tyrosine, and the neuromodulator histamine is a histidine derivative.

Similarities between chemotactic signals that trigger signaling at chemosensory synapses and the neurotransmitter signals that activate canonical synapses also extend to other essential nutrients. For example, *C. elegans* can chemotax effectively towards choline[13], a precursor of the essential membrane lipid phosphatidylcholine[14], and the simple choline derivative acetylcholine (ACh) is a key neurotransmitter at the neuromuscular junction and at neuron-neuron synapses. Chemosensory neurons are also potent detectors of pH, as demonstrated by chemosensory-neuron-dependent avoidance of high proton concentrations in *C. elegans*[15]. Similarly, in *C. elegans*, protons can also serve as transmitters for muscle contraction[16]. Although in this case protons are released from intestinal cells, and not from a classical presynaptic terminus, they are nevertheless acting in the capacity of a transmitter. Thus, many important neurotransmitters are derivatives of or are themselves well-established sensory stimuli (Figure 1).

Postsynaptic similarities

Given that chemosensory synapses mirror canonical synapses in the cues they can detect, it may not be surprising to find that these similarities extend to the physical structures used for detection. At excitatory neuronal synapses, dendritic spines are the major components of postsynaptic neuronal architecture; whereas at chemosensory synapses most signal detection takes place within specialized chemosensory receptive endings residing at dendritic tips or at tips of specialized sensory cells. These structures are the major localization sites for

neurotransmitter receptors and environmental receptors, respectively, and house signal transduction molecules and ion channels crucial for stimulus transmission.

Polarity and Trafficking

Both chemosensory and postsynaptic synaptic sites reside in apically polarized domains of their respective cells. It is presently unknown whether specification of these structures is guided by common polarity signals; however, axonal termini of at least some chemosensory neurons and central neurons are specified by shared mechanisms. For example, the kinase SAD-1 and its binding partner Neurabin are required for localizing presynaptic components to axons in both chemosensory and postsynaptic neurons[17,18], and in *C. elegans*, *sad-1* mutants inappropriately accrete presynaptic components within dendrites of both sensory neurons and motorneurons. These results suggest that formation of polarized structures that promote receptive ending formation, may also be under common control in these two cell types.

Trafficking of receptors and other signaling proteins is thought to be governed by pre-existing polarity cues. Some trafficking components seem to be used to deliver both chemosensory and neurotransmitter receptors to their respective dendritic compartments. For example, the *C. elegans* μ1 subunit of the clathrin adaptor complex AP1 is required for localizing both odorant receptors in sensory neurons[19] and neurotransmitter receptors in postsynaptic neurons[20]. Similarly, the small GTPase Rab11 is required in *Drosophila* for rhodopsin localization to apical membranes[21], and in rats for localization of AMPA receptors to postsynaptic membranes[22]. These similarities suggest not only relatedness in cargo, but also strengthen the possibility that polarity cues involved in generating sensory and postsynaptic signaling structures are related.

Signaling compartments

At first glance, chemosensory receptive endings and dendritic spines may appear only superficially similar: although both are cytoskeleton-rich membrane specializations, chemosensory receptive endings are often non-motile cilia that depend on microtubules for their structure[23], while spine morphology is thought to be governed by actin[24]. However, several observations suggest these distinctions are not so clear-cut. Some chemosensory cells do not utilize cilia for signal detection. For example, taste receptor cells in mammals terminate in microvilli containing actin and actin binding Espin proteins[25,26]. Other sensory cells also use microvilli instead of cilia. For example, although sensory hair cells in the inner ear each contain a single microtubule-based kinocilium, mechanosensation is thought to take place primarily in the numerous stereocilia, which like spines are composed of actin[27,28]. A similar cellular architecture characterizes the *C. elegans* thermosensory neuron AFD, which possesses a single microtubule-based cilium surrounded by an array of microvilli-like protrusions lacking microtubules, and presumably supported by actin[29,30]. Loss of these microvilli but not of the cilium as a result of mutations in the gene *ttx-1* or by ablation of neighboring glia is associated with thermosensory deficits[31,32]. Thus, actin is no stranger to sensory receptive endings. Conversely, microtubules may have a role to play at dendritic spines. A recent report suggests that microtubules are important regulators of dendritic spine morphology and interact through the microtubule-associated protein EB3 with the p140Cap/SNIP protein, which is enriched at the postsynaptic density (PSD)[33]. These observations suggest that the paradigm that dendritic spines use actin and sensory endings use microtubules is an oversimplification.

Regardless of whether postsynaptic and sensory structures employ actin or microtubules, a functional comparison suggests that both types of protrusions serve similar roles. Dendritic spines are chemically isolated compartments that are highly malleable in size and shape[34].

Where examined, spine volume correlates well with the degree of presynaptic activity[35], and spine size and shape is responsive to developmental and homeostatic cues. For example, the number and density of dendritic spines of hippocampal neurons varies dramatically with estrogen levels in rats[36,37]. Likewise, chemosensory cilia and microvilli are chemically isolated compartments that are also morphologically malleable. In *C. elegans*, for example, the shape of the ciliated endings of the AWB chemosensory neurons is affected by the presence of chemosensory stimuli[38], and mutations blocking sensory signal transduction promote alteration of cilia membrane shape, suggesting a feedback mechanism that may also operate in dendritic spines[34]. Furthermore, the shapes of the *C. elegans* AWC and AFD ciliated endings vary dramatically in response to pheromone-triggered developmental cues[39].

Shared functions for sensory receptive endings and postsynaptic structures are also suggested by studies of the *C. elegans* gene *daf-19*. This gene has long been studied as a regulator of ciliogenesis, and its product, a conserved RFX transcription factor, binds directly upstream of many genes expressed in ciliated neurons[40]. A new study suggests that an alternatively-spliced form of the same gene is responsible for the resistance of *daf-19* mutant animals to the paralytic effects of aldicarb, an ACh esterase inhibitor, and levamisole, an ACh receptor agonist. Resistance to these agents, specifically to levamisole, is a telltale sign of postsynaptic defects, suggesting that in addition to its roles in sensory neurons, *daf-19* also functions in postsynaptic cells[41].

Receptors

The architectural and functional parallels between sensory receptive endings and dendritic spines reflect the even more remarkable similarities between the chemosensory receptors and neurotransmitter receptors that decorate these structures (Figures 1 and 2). Neurotransmitter receptors are classified as slow (metabotropic) or fast (ionotropic) receptors[1]. Many of the metabotropic neurotransmitter receptors (including serotonin receptors, dopamine receptors, and the muscarinic acetylcholine receptor) are G-protein coupled receptors (GPCRs)[42]. Similarly, GPCRs serve as receptors for chemosensory stimuli including odorants and tastants in vertebrates and in *C. elegans*[43,44], and light (rhodopsin)[45] in many organisms. Importantly, GPCRs are used by mice and zebrafish to detect amino acids[9,10], and it is likely that amino-acid detection in *C. elegans* also employs this receptor class.

Ionotropic receptors fall into a number of classes, including those represented by glutamate and acetylcholine (ACh) receptors. *C. elegans* DEG-3, a member of the nicotinic ACh receptor family, is, surprisingly, not found at synapses, but is localized to sensory receptive endings of the IL2 sensory neurons, and is required for chemotaxis towards choline[13]. Similarly, a recent study in *Drosophila* revealed that proteins of the ionotropic glutamate receptor family are housed in sensory cilia of olfactory neuron dendrites, and respond to environmental stimuli[5] (Figure 2).

Neurotransmitter receptors at postsynaptic sites are usually anchored by large molecular weight scaffolds. These scaffolds commonly contain proteins with PDZ (Postsynaptic density 95, Discs large, and Zonula occludens-1) domains[46]. Similarly, some sensory receptive endings also feature scaffolds that serve to hold signaling proteins in place. In *Drosophila*, phototransduction is mediated through a PDZ-containing scaffold called the INAD (inactivation-no-afterpotential D) macromolecular complex[47]. Although other components of this scaffold may differ from classic postsynaptic density components, the presence of a macromolecular assembly, and specifically of PDZ domains, suggest similar functions. PDZ proteins PSD95 and Veli-2 have also been found in association with the

chemosensory transduction protein Ggamma13 in taste cells[48]; however, the functional significance of this interaction has not been established.

Together, these observations suggest that receptive endings on sensory neurons and postsynaptic dendritic spines share not only morphological and functional characteristics, but also possess similar molecular components.

Glial similarities

Of the cellular constituents of the neuronal synapse, perhaps the least is known about the glia that ensheath this structure. Nonetheless, recent studies are consistent with the idea that glia associated with neuron-neuron synapses and those associated with sensory receptive structures share functional and molecular characteristics[49].

Most vertebrate excitatory neuronal synapses are ensheathed by astrocyte processes[2,3,50], and most neuromuscular junctions are ensheathed by perisynaptic Schwann cells[51]. Likewise, invertebrate and vertebrate sensory receptive endings are generally associated with glia or glia-like cells: the retinal pigmented epithelium is associated with photoreceptor cells in the eye, sustentacular cells associate with olfactory neurons in the nose, and Deiters' cells surround the hair cells of the inner ear. All three cell types possess properties and express proteins suggestive of glial character. For example, like astrocytes, retinal pigmented epithelial cells and sustentacular cells have important phagocytic functions[52,53]. Sustentacular cells are electrically coupled and, like astrocytes, exhibit complex calcium ion dynamics when stimulated by ATP[53], and like some astrocytes in adult animals, sustentacular cells can give rise to neurons[54]. Deiters' cells, like astrocytes, are thought to regulate extracellular potassium ion levels[55], and express Glial Fibrillary Acidic Protein (GFAP), an intermediate filament protein that often serves as an astrocytic marker[56]. All glia in *C. elegans* associate with sensory neuron receptive endings, and some fully ensheath these endings[30], an architecture also seen in the murine Grueneberg ganglion, which is thought to have sensory capacity and whose neuron-ensheathing glia are also GFAP positive[57,58]. Preliminary evidence suggests that all *C. elegans* glia express ion transporters, including a potassium chloride transporter (M. Katz and S. Shaham, unpublished), and may, like their vertebrate counterparts, control the ionic environment of sensory cilia.

An increasing body of evidence suggests that synaptic glia are essential for synaptic transmission and that glia modulate firing responses of postsynaptic neurons by secreting neurotransmitter inhibitors or receptor antagonists[59,60] (Box 1). Similarly, in *C. elegans*, the glia associated with the amphid sensory organ are essential for sensory neuron function, as demonstrated by the profound sensory deficits exhibited by animals in which these glia have been ablated[32]. Vertebrate glia are also important for synaptogenesis, and recent studies have implicated astrocyte-released thrombospondin as a key mediator of this effect[61]. Intriguingly, in *C. elegans*, the glia associated with sensory neurons secrete a protein, FIG-1, containing thrombospondin type I and EGF-like type II domains, both of which are present in thrombospondin. Furthermore, FIG-1 modulates the physical and functional properties of sensory neurons[32]. Perhaps the most suggestive evidence for a functional correspondence between glia at sensory receptive endings and those at neuronal synapses is revealed by the anatomy of the *C. elegans* CEPsh glia (Figure 3). These bipolar cells send thin anterior processes towards the tip of the animal's nose, where they ensheath the receptive endings of the CEP neurons[30] (as well as the CEM neurons in males). CEPsh glia play an important role in CEP neuron dendrite extension[62], and are presumably important for CEP neuron sensory responses. From their posterior surfaces, CEPsh glia project large sheet-like processes that wrap around the nerve ring, the main neuropil of the animal, and extend processes that are in physical proximity to at least some neuron-neuron synapses[63] (Figure

3). Although this arrangement- in which a single glial cell contacts both a sensory receptive ending and a canonical synapse- might result from anatomical happenstance, when taken together with the evidence described above, it is highly suggestive of functional similarities between these structures.

Conclusions

The similarities in functional logic, morphology, and molecular biology between neuronal synapses and sensory structures raise the possibility that these entities may have shared a common evolutionary origin. However, as with any speculative evolutionary argument, independent convergence of these structures as a result of common requirements for localized signaling cannot be ruled out. In many invertebrates, sensory-motor neurons, single neurons that respond to the environment and that also contact muscles directly, are common. For example, *C. elegans* inner labial neurons contain dendritic ciliated sensory endings and synapse through their axons onto head muscles[63]. Likewise, gastrodermal sensory neurons of hydra respond to ingested food cues with an apical cilium, and synapse onto muscle cells using an axonal protrusion[64]. These hybrid cells might represent an ancestral neuron class from which both sensory and postsynaptic neurons evolved. If indeed both structures did arise from a shared ancestral structure, studies of the demosponge *Amphimedon* hint at what such a preneural structure might have looked like. Genomic studies of this sponge, which lacks neurons, reveal that it possesses a large number of postsynaptic gene homologues, many of which resemble proteins associated with the vertebrate postsynaptic density[65]. These proteins are preferentially expressed in the larval flask cell[65], which possesses a well-defined cilium, and is thought to have environmental sensing capacity[66]. Thus, an ancient cell akin to the flask cell might have served as the pre-neural ancestor of both postsynaptic and sensory neurons. Evidence that postsynaptic components in the flask cell are required for sensory transduction in this cell would bolster this hypothesis. Alternatively, it is also possible that an evolutionary precursor of chemosensory and postsynaptic neurons was a cell type designed to measure the internal environment of an animal. The recent description of olfactory receptor proteins on motile cilia in the airway of humans[67] would be consistent with such a model.

Regardless of their evolutionary origins, however, the similarities between sensory receptive structures and neuronal synapses described here suggest the tantalizing possibility that our understanding of neuronal synapse biology may be greatly informed by an understanding of sensory organ function. It is even conceivable that the mechanistic underpinnings of memory acquisition and storage might be revealed at sensory receptive endings. In this respect it is of note that some learning paradigms in *C. elegans* seem to be associated with changes in sensory neurons, and not downstream interneurons. For example, prolonged exposure to some attractive sensory stimuli promotes behavioral adaptation to the stimulus that can persist for up to 24 hours. This response reflects a specific effect on sensory neuron output, as it is mediated by the cGMP-dependent kinase EGL-4, functioning within the relevant sensory neurons. Specifically, upon continuous exposure to stimulus, EGL-4 localization shifts from cilia to sensory-neuron nuclei to affect gene expression, a process that has been shown to be important for adaptation[68-70]. This adaptation phenomenon is reminiscent of synaptic phenomena including long-term potentiation[71] (LTP) and depression (LTD) in which repetitive presynaptic stimulation, followed by neurotransmitter release, alters postsynaptic output over a time scale of hours or days. In the case of LTP, postsynaptic effects are also mediated by a cyclic nucleotide second messenger (cAMP)[72], and translocation of nuclear import proteins, importins, carrying unknown cargo from synaptic sites to the nucleus correlates with LTP in hippocampal slices[73]. However, many details differ between these phenomena and at this point it is too early to tell whether they represent different facets of a common underlying mechanisms.

LTP and LTD may be correlates of memory formation, however, whether this is indeed the case remains highly debated. Although these phenomena can be induced at specific synapses, correlating synaptic changes with memory alteration at the level of the animal has been challenging. This reflects a general difficulty in correlating alterations at specific synapses with animal behavior. In this respect, sensory organs offer a distinct advantage. They are physically easy to engage, as they are generally exposed to the environment, and the effects of their manipulation on animal behavior are easy to assay. Furthermore, sensory neuron stimulation can be controlled using natural cues, and unlike many studies of neuron-neuron synapses, does not require non-native electrical stimulation of presynaptic cells.

Although the chemosensory synapse and the neuronal synapse are distinct entities in the nervous system, they possess similarities that go well beyond what one might expect from generic signaling platforms. Other signaling systems, such as hormone signaling pathways and immune signaling, use GPCRs, peptide ligands, and accessory cells; however, the striking conservation in the molecular details of these components between chemosensory and neuron-neuron synapses suggests a deeper relationship between these two structures. Both chemosensory and neuron-neuron synapses use similar ligands (e.g. amino acids), both structures use similar subclasses of receptors (e.g. ionotropic glutamate receptors), and both structures employ glia with similar properties as vital accessory cells. While many of the examples in this review are drawn from studies of *C. elegans* and *Drosophila*, the remarkable conservation of chemosensory organ morphology and molecular biology throughout the animal kingdom suggests that these similarities are likely broadly conserved. Consideration of these similarities might shed light on important synaptic processes such as signal integration, modulation of dendritic spine morphology, and glia-neuron communication, and might help to elucidate developmental programs that give rise to both structures to reveal the basic operating principles of all synapses.

Box 1. Glial functions at the synapse

Efforts to understand roles played by glia at the synapse have begun to reveal the developmental and functional importance for these cells at this information transfer site. Developmentally, glia-derived factors, including cholesterol[74] and the secreted protein thrombospondin[61] promote synapse formation; and phagocytic functions of glia seem to participate in synaptic remodeling at the neuromuscular junction[75]. Glia also seem to play important roles in defining and positioning synaptic sites during development in C. elegans[76], and have been reported to regulate dendritic spine shape in the mouse through Eph signaling[77]. Although the functions of glia at synapses are not fully understood, they have been implicated in the regulation of a number of processes likely to affect synaptic efficacy. Glial cells express a variety of neurotransmitter transporters, including those for glutamate[78], glycine[79], and GABA[80]. Evidence that glia secrete neurotransmitters, including glutamate[81], acetylcholine[82], GABA[83], and ATP[84], has also been reported, suggesting possible direct effects of glia on postsynaptic targets. Glia also produce neurotransmission inhibitors, and these have been shown to have important functional consequences in specific settings. For example, a glia-derived acetylcholine receptor mimic attenuates cholinergic signaling in the fresh water snail, and D-serine, an NMDA receptor antagonist, is released by astrocytes, and may influence glutamatergic signaling in the CNS[85].

Although the characterization of synaptic glia is well on its way, molecular studies of sensory organ glia have lagged behind. However, recent efforts to fill this gap by examining transcripts enriched in glia associated with sensory synapses in C. elegans have yielded intriguing gene lists[32]. In these lists are found genes encoding proteins containing thrombospondin type I domains, transporters related to GABA transporters,

neurotransmitter-like peptides, glutamate receptors, and transporters involved in ion homeostasis. If validated, these similarities may further strengthen the idea that glia at sensory and neuronal synapses share common activities. Furthermore, studies of C. elegans sensory organ glia reveal key roles for these cells in regulating sensory neuron receptive ending morphology[32], a phenomenon reminiscent of spine morphology control by astrocytes.

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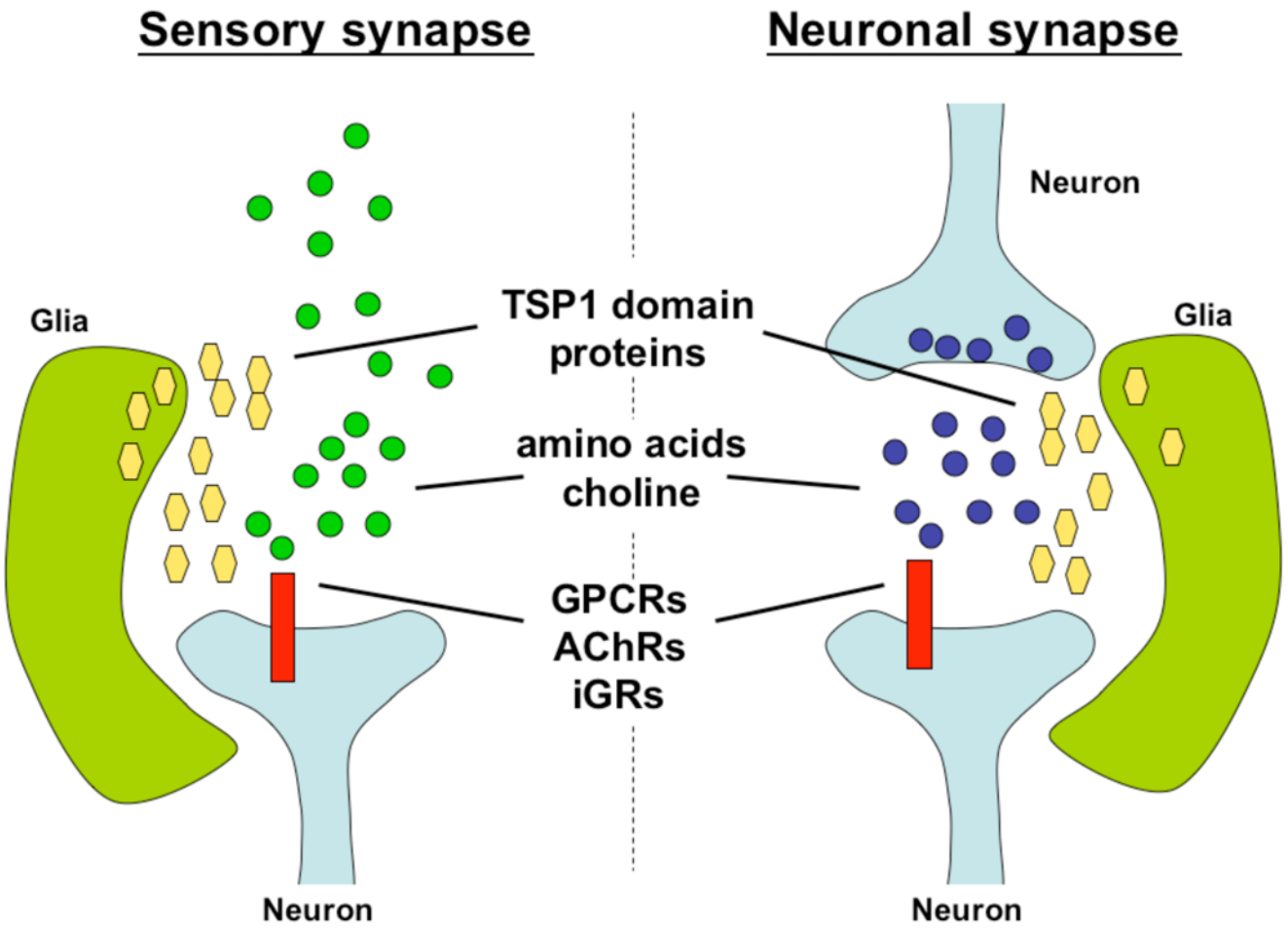

Figure 1. Similarities between sensory receptive endings and neuron-neuron synapses

Structural and molecular similarities between sensory receptive endings and neuronal synapses are depicted. Both structures share commonalities in the ligands (amino acids, choline), in the receptors (GPCRs, AChrs, and iGRs), and in glial secreted proteins required for synaptic function (TSP1 domain proteins). Blue circles, neurotransmitters. Green circles, environmental nutrients. Yellow hexagons, thrombospondins and related proteins. Red rectangles, receptors for either neurotransmitters or environmental nutrients.

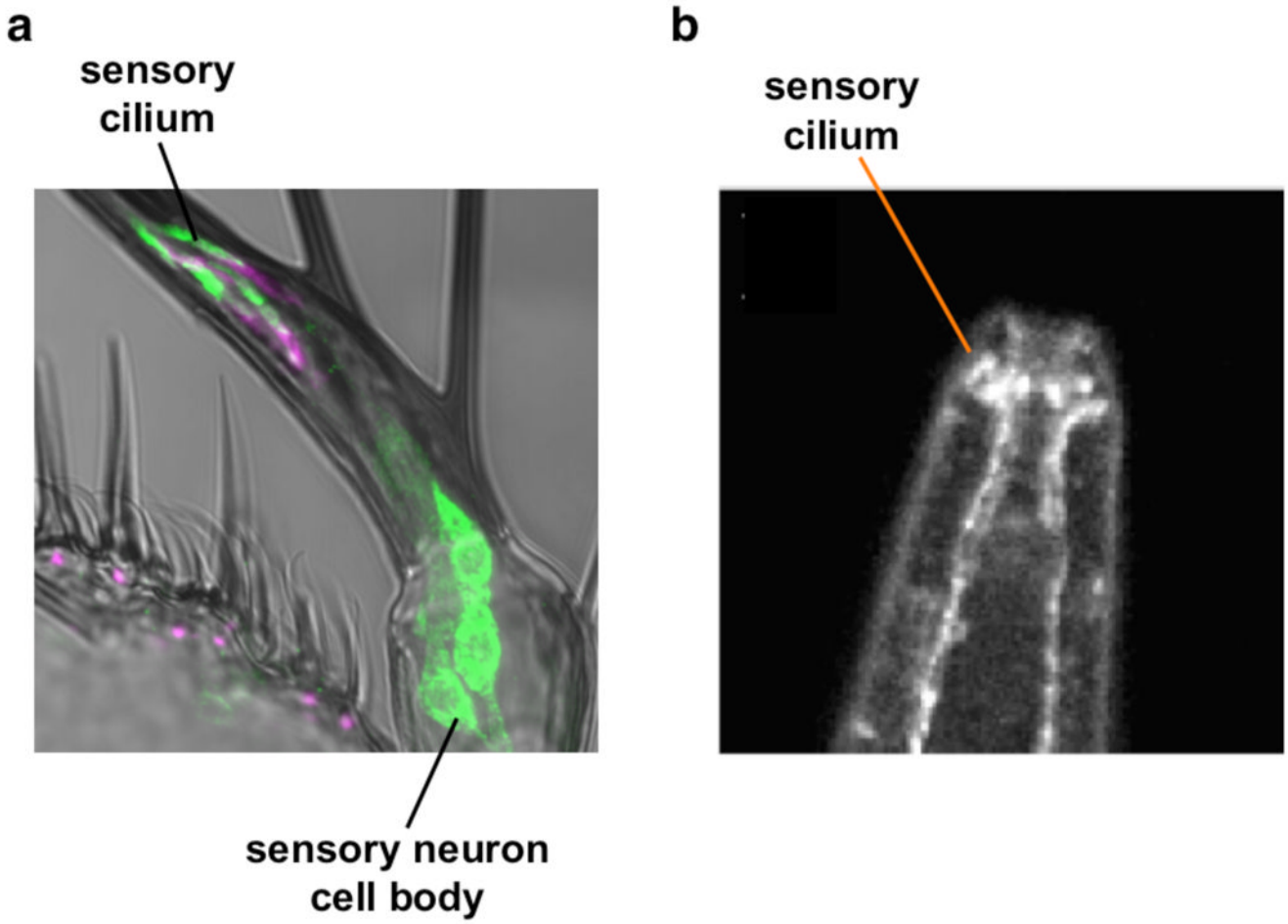

Figure 2. Neurotransmitter receptor-related proteins are expressed at sensory receptive endings
a, Immunostaining against the ionotropic glutamate receptor-like protein IR25a (green) demonstrating its localization to cilia and cell bodies of aristal sensory neurons in *Drosophila*. The ciliary base is marked with antibody mAb 21A6 (magenta). Figure generously provided by Dr. Richard Benton. Scale bar, 10 μm. **b**, Immunostaining against the *C. elegans* DEG-3 nACh receptor shows localization to sensory endings in the nose of the animal. Image reproduced with permission from [ref. 13].

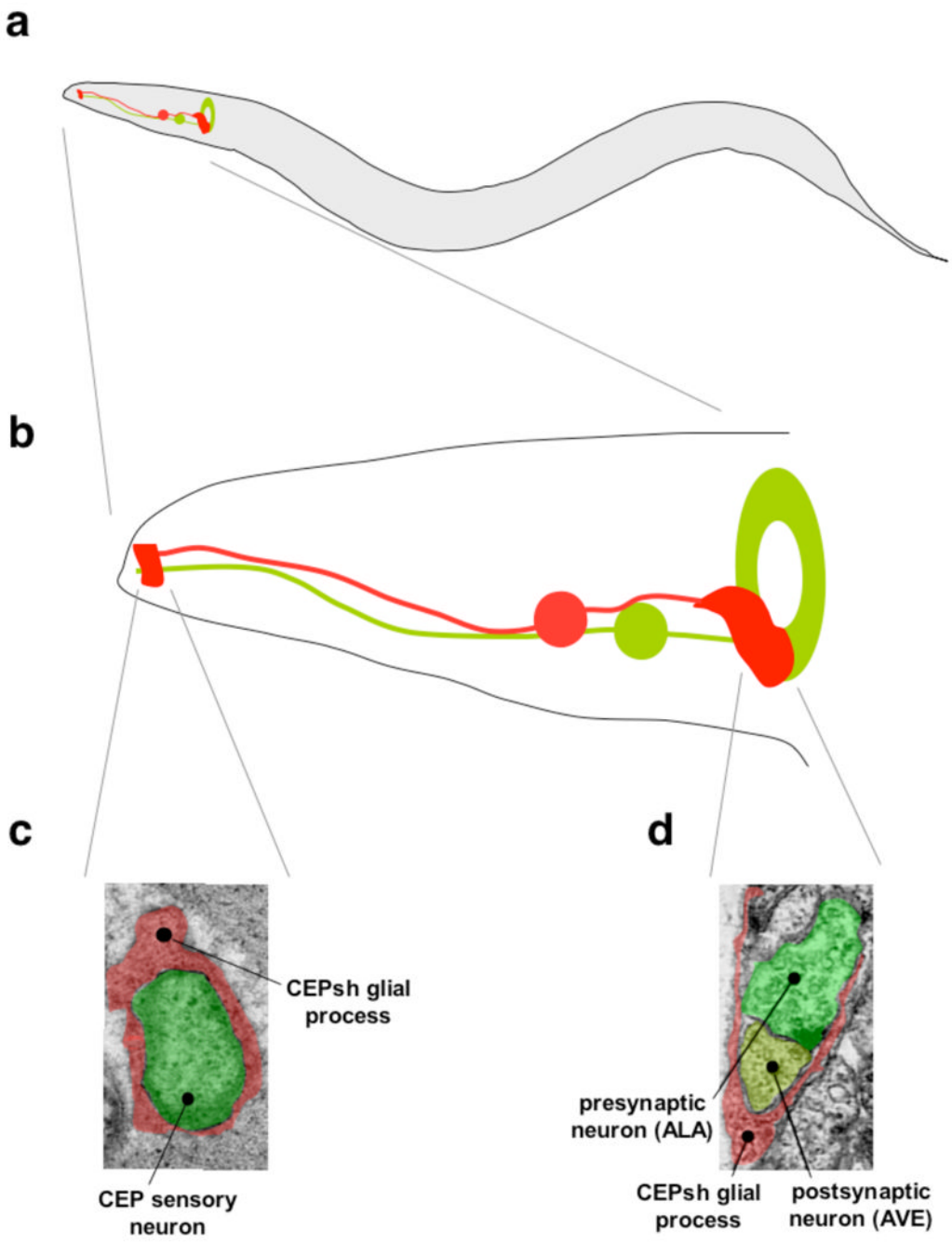

Figure 3. *C. elegans* CEPsh glia envelop sensory and neuron-neuron synapses

a, Schematic diagram of a *C. elegans* adult depicting the position of the nerve ring (green doughnut) where most synaptic contacts are located, one of the CEP sensory neurons (green line, neuronal processes, green circle, cell body), and the CEPsh glia (red). **b**, Magnified view of the head region depicted in **a. c**, An electron micrograph of a cross section of the *C. elegans* nose demonstrating the ensheathment of a CEP neuron sensory ending (green) by a CEPsh glial process (red) (Y. Lu and Shaham, unpublished). **d**, An electron micrograph depicting ensheathment of a neuronal synapse between the ALA (green) and AVE neurons (yellow-green) by CEPsh glia processes (red). Note the presence of a characteristic

presynaptic density (black triangular spot) at the lower right portion of the ALA neuron. Image obtained with permission from [ref. 63].