OPINION

Chemosensory organs as models of neuronal synapses

Shai Shaham

Abstract | Neuronal synapses are important microstructures that underlie complex cognitive capacities. Recent studies, primarily in *Caenorhabditis elegans* and *Drosophila melanogaster*, have revealed surprising parallels between these synapses and the 'chemosensory synapses' that reside at the tips of chemosensory cells that respond to environmental stimuli. Similarities in the structures, mechanisms of action and specific molecules found at these sites extend to the presynaptic, postsynaptic and glial entities composing both synapse types. In this article I propose that chemosensory synapses may serve as useful models of neuronal synapses, and consider the possibility that the two synapse types derive from a common ancestral structure.

Neuronal synapses, the physical structures that connect neurons to each other, are major sites of information processing in the nervous system. These synapses are composed of presynaptic and postsynaptic 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 the release and reuptake of neurotransmitters and by determining the neurotransmitters' chemical structure. Postsynaptic termini influence neurotransmitter efficacy by controlling recognition through surface receptors, by inhibiting neurotransmitter activity (chemically or competitively) and by integrating multiple neurotransmitter signals from one or more 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.

Chemosensory organs are also important sites of information processing. Environmental stimuli are encountered at these structures, and these signals are interpreted in sensory cells before being passed 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, including chemosensory neurons, display adaptation aimed at blunting the response to repetitive stimuli. The sensory capacities of modern organisms are elaborate and diverse. Although it is unclear whether all sensory organs evolved from a common ancestral structure, some are likely to have evolved from a system tasked primarily with detecting environmental chemicals. Indeed, intriguing similarities between one class of animal and plant chemoreceptors and bacterial proteins responsible for detecting environmental chemicals[5–7] have been described, suggesting that chemosensation is an ancient sensory modality.

Recent studies, primarily in the nematode *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster*, have revealed interesting commonalities in the logic, organization and molecular machinery used by chemosensory receptive structures and neuronal synapses. In both systems, 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, resulting in 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 signalling, the similarities between chemosensory organs and synapses go beyond generic parallels in signal transduction. Surprising molecular similarities have been discovered between chemosensory structures and synapses at each level: the small-molecule signals, the specialized receptive compartments, the identities of the receptors and even the neighbouring glia that surround each structure (FIG. 1). These striking parallels suggest that 'chemosensory synapses' and perhaps 'sensory synapses' in general (not to be confused with the neuron–neuron synapses between sensory neurons and downstream interneurons) may be used to guide our understanding of neuron–neuron synapses. In this article, I primarily explore the similarities between chemosensory receptive structures and neuron–neuron synapses, but also draw some parallels with structures associated with other sensory modalities.

Presynaptic similarities

Although termini of chemosensory cells are not associated with a physical presynaptic structure, there are parallels between the environmental food-related cues detected by chemosensory cells and presynaptically released neurotransmitters. For example, *C. elegans*, zebrafish and mice can sense and chemotax towards amino acids[8–10]. Likewise, humans can taste amino acids (the umami basic taste) and are particularly sensitive to 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 (γ-aminobutyric acid), two major inhibitory neurotransmitters. Other neurotransmitters, including serotonin, dopamine, adrenaline, noradrenaline, 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 signalling at chemosensory synapses and the neurotransmitter signals that activate canonical synapses also extend to other essential nutrients. For example, *C. elegans* can chemotax towards choline[13], a precursor of the essential membrane lipid phosphatidylcholine[14], and the simple choline derivative acetylcholine 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 serve as transmitters for muscle contraction[16]. Although in this case the protons are released from intestinal cells, rather than 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 (FIG. 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 the postsynaptic neuronal architecture, whereas at chemosensory synapses most signal detection takes place in specialized chemosensory receptive endings residing at dendritic tips or at the 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 sites reside in apically polarized domains of their respective cells. At present, it is unknown whether the specification of these structures is guided by common polarity signals; however, the axonal termini of at least some chemosensory neurons and central neurons are specified by shared mechanisms. For example, the kinase SAD1 (also known as BRSK1) and its binding partner neurabin are required for the localization of presynaptic components to axons in both chemosensory and postsynaptic neurons[17,18], and in *C. elegans*, *sad-1* mutants inappropriately accrete presynaptic components in the dendrites of both sensory neurons and motor neurons. These results suggest that the 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 signalling 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 the localization of both odorant receptors in sensory neurons[19] and neurotransmitter receptors in postsynaptic neurons[20]. Similarly, the small GTPase RAB11 is required in *D. melanogaster* for the localization of rhodopsin to apical membranes[21] and in rats for the localization of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors to postsynaptic membranes[22]. These similarities suggest that the cargoes trafficked by these proteins in sensory and neuronal synapses are related and also strengthen the possibility that the polarity cues involved in generating sensory and postsynaptic signalling structures are related.

Signalling compartments. At first glance, chemosensory receptive endings and dendritic spines may seem 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], whereas dendritic spine morphology is thought to be governed by actin[24]. However, several observations suggest that these distinctions are not so clear-cut. Some chemosensory cells do not use 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 that lack microtubules and are presumably supported

Box 1 | **Glial functions at the synapse**

Efforts to understand the roles that glia have at the synapse have begun to reveal the developmental and functional importance of these cells at this information transfer site.

Developmentally, glia-derived factors, including cholesterol[74] and the secreted protein thrombospondin[61], promote synapse formation, whereas the phagocytic functions of glia seem to participate in synaptic remodelling at the neuromuscular junction[75]. Glia also seem to have 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 ephrin signalling[77].

Although the functions of glia at synapses are not fully understood, they have been implicated in the regulation of several processes that are likely to affect synaptic efficacy. Glial cells express various neurotransmitter transporters, including those for glutamate[78], glycine[79] and GABA (γ-aminobutyric acid)[80]. Evidence that glia secrete neurotransmitters, including glutamate[81], acetylcholine[82], GABA[83] and ATP[84], has also been reported, suggesting that glia have direct effects 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 signalling in the freshwater snail, and D-serine, an NMDA (*N*-methyl-D-aspartate) receptor antagonist, is released by astrocytes and may influence glutamatergic signalling 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 *Caenorhabditis 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 have 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 that is reminiscent of spine morphology control by astrocytes.

by actin[29,30]. Loss of these microvilli but not of the cilium as a result of mutations in the gene *ttx-1* or ablation of neighbouring glia is associated with thermosensory deficits[31,32]. Thus, actin is no stranger to sensory receptive endings. Conversely, microtubules may have a part 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 protein p140Cap (also known as SNIP), which is enriched at the postsynaptic density[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 use actin or microtubules, a functional comparison suggests that the two types of protrusions have 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 are responsive to developmental and homeostatic cues. For example, the number and density of dendritic spines on hippocampal neurons vary dramatically with oestrogen levels in rats[36,37]. Likewise, chemosensory cilia and microvilli are also chemically isolated compartments that are 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 the existence of 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 (regulatory factor X) 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 acetylcholinesterase inhibitor, and levamisole, an acetylcholine receptor agonist. Resistance to these agents, particularly to levamisole, is a telltale sign of postsynaptic defects,

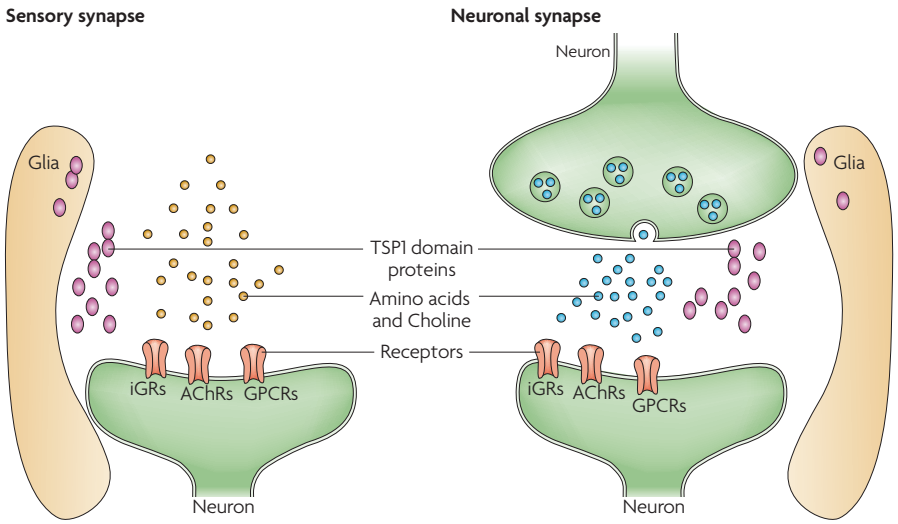

Figure 1 | **Similarities between sensory receptive endings and neuron–neuron synapses.** Structural and molecular similarities between sensory receptive endings and neuronal synapses. The two structures have commonalities in their ligands (amino acids and choline), receptors (G protein-coupled receptors (GPCRs), acetylcholine receptors (AChRs) and ionotropic receptors (iGRs)) and glial secreted proteins required for synaptic function (TSP1 domain proteins). Blue circles represent neurotransmitters; yellow circles represent environmental nutrients.

suggesting that, in addition to its roles in sensory neurons, *daf-19* functions in postsynaptic cells[41].

Receptors. The architectural and functional parallels between sensory receptive endings and dendritic spines are accompanied by even more remarkable similarities between the chemosensory receptors and neurotransmitter receptors that decorate these structures (FIGS 1,2). Neurotransmitter receptors are classified as slow (metabotropic) or fast (ionotropic) receptors[1]. Many metabotropic neurotransmitter receptors (including serotonin receptors, dopamine receptors and muscarinic acetylcholine receptors) 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] as well as 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 uses this receptor class.

Ionotropic receptors fall into several 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 *D. melanogaster* revealed that proteins of the ionotropic glutamate receptor family are housed in the sensory cilia of olfactory neuron dendrites and respond to environmental stimuli[5] (FIG. 2).

Neurotransmitter receptors at postsynaptic sites are usually anchored by high-molecular-mass 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 signalling proteins in place. In *D. melanogaster*, phototransduction is mediated through a PDZ domain-containing scaffold known as the INAD (inactivation-no-afterpotential D) macromolecular complex[47]. Although other components of this scaffold may differ from those of the classic postsynaptic density, the presence of a macromolecular assembly, and specifically of PDZ domains, suggests similar functions. The PDZ proteins PSD95 (also known as DLG4) and Veli-2 (also known as Lin-7B) 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 cells and postsynaptic dendritic spines not only share morphological and functional characteristics but also possess similar molecular components.

Glial similarities

Of the cellular constituents of the neuronal synapse, perhaps least is known about the ensheathing glia. 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 that are 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 Ca^{2+} dynamics when stimulated by ATP[53] and, like some astrocytes in adult animals, can give rise to neurons[54]. Deiters' cells, like astrocytes, are thought to regulate extracellular K^+ levels[55], and they 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]. A similar architecture is also seen in the murine Grueneberg ganglion, which is thought to have sensory capacity and contains neuron-ensheathing glia that express GFAP[57,58]. Preliminary evidence suggests that all *C. elegans* glia express ion transporters, including a K^+–Cl^- transporter (S.S., unpublished observations), 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 the 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 being a key mediator of this effect[61]. Intriguingly, in *C. elegans* the glia associated with sensory neurons secrete a protein, FIG-1, that contains thrombospondin type I and epidermal growth factor (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 (FIG. 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 have 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] (FIG. 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.

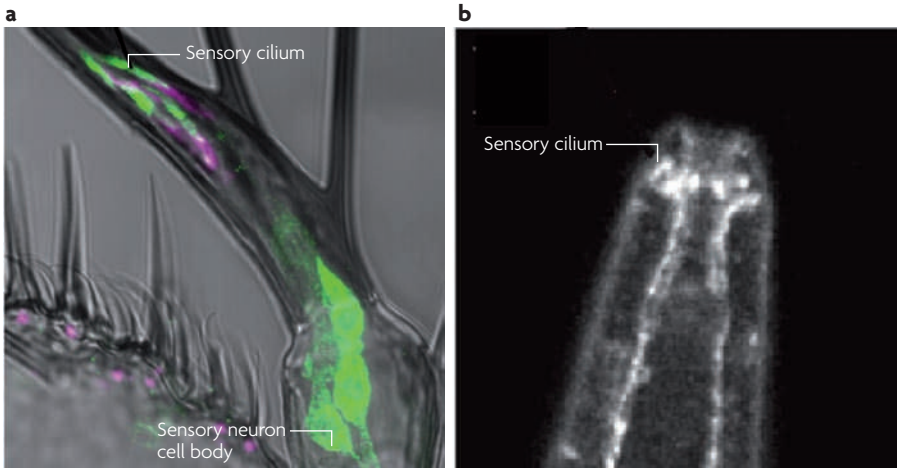

Figure 2 | **Neurotransmitter receptor-related proteins are expressed at sensory receptive endings. a** | Immunostaining against the ionotropic glutamate receptor-like protein IR25a (green), demonstrating its localization to the cilia and cell bodies of aristal sensory neurons in *Drosophila melanogaster*. The ciliary base is marked with mAb 21A6 antibody (magenta). **b** | Immunostaining against the *Caenorhabditis elegans* DEG-3 nicotinic acetylcholine receptor shows its localization to sensory endings in the nose of the animal. Part **a** is courtesy of R. Benton, University of Lausanne, Switzerland. Part **b** is reproduced, with permission, from REF. 13 © (2001) Academic Press.

Conclusions

The similarities in functional logic, morphology and molecular biology between neuronal synapses and sensory structures raise the possibility that these entities may have a common evolutionary origin. However, as with any speculative evolutionary argument, independent convergence of these structures as a result of common requirements for localized signalling 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 they 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 the two structures did arise from a shared ancestral structure, studies of the demosponge *Amphimedon* hint at what such a preneuronal structure might have looked like. Genomic studies of this sponge, which lacks neurons, reveal that it possesses a large number of postsynaptic gene homologues, the products of 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-neuronal 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 that measured 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 rather than downstream interneurons. For example, prolonged exposure to some attractive sensory stimuli promotes behavioural 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 cyclic GMP-dependent kinase EGL-4, functioning within the relevant sensory neurons. Specifically, on 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 long-term depression (LTD) in which repetitive presynaptic stimulation, followed by neurotransmitter release, alters postsynaptic output over a timescale of hours or days. In the case of LTP, postsynaptic effects are also mediated by a cyclic nucleotide second messenger (cyclic AMP)[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 it is too early to tell whether they represent different facets of a common underlying mechanism.

LTP and LTD may be correlates of memory formation, but this 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 behaviour. 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 behaviour 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.

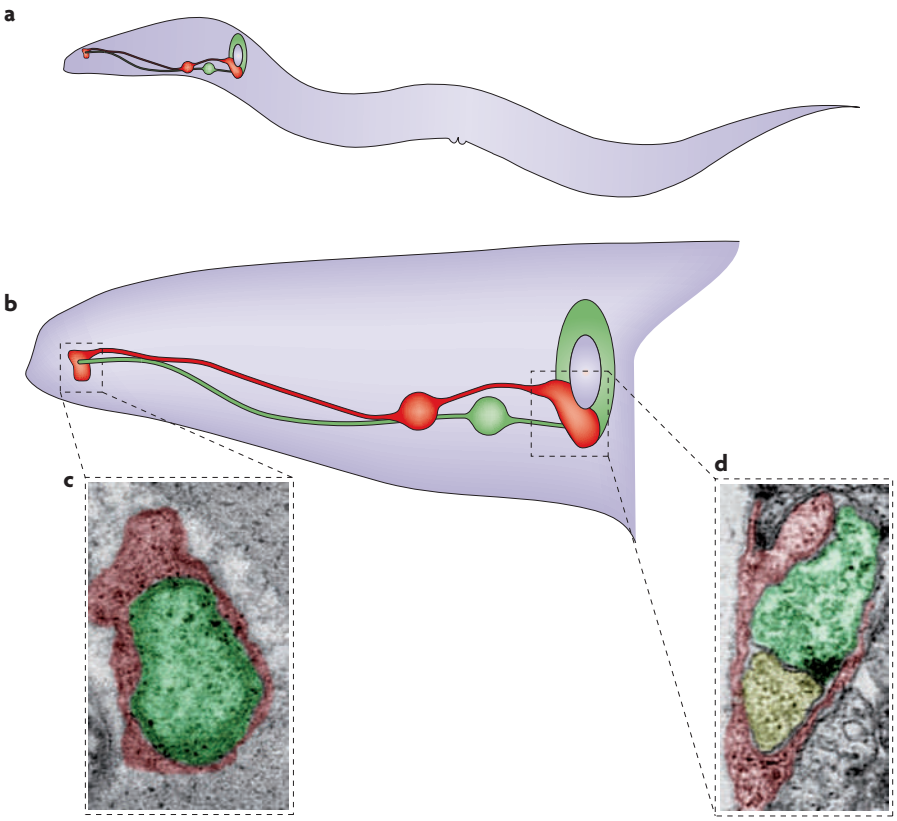

Figure 3 | ***C. elegans* CEPsh glia envelop sensory and neuron–neuron synapses. a** | The position, in a *Caenorhabditis elegans* adult, of the nerve ring (green ring), where most synaptic contacts are located. One of the CEP sensory neurons (green) and the CEPsh glia (red) are depicted. **b** | Magnified view of the head region depicted in part **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). **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. Part **d** is reproduced, with permission, from REF. 63 © (1986) Royal Society of London.

Summary

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 signalling platforms. Other signalling systems, such as hormone signalling pathways and immune signalling, use GPCRs, peptide ligands and accessory cells, but the striking conservation in the molecular details of these components between chemosensory and neuron–neuron synapses suggests a deeper relationship between these two structures. Chemosensory and neuron–neuron synapses use similar ligands (such as amino acids), use similar subclasses of receptors (such as ionotropic glutamate receptors) and use glia with similar properties as vital accessory cells. Although many of the examples in this article are drawn from studies of *C. elegans* and *D. melanogaster*, the remarkable conservation of chemosensory organ morphology and molecular biology throughout the animal kingdom suggests that these similarities are likely to be 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 programmes that give rise to both structures to reveal the basic operating principles of all synapses.

Laboratory of Developmental Genetics, The Rockefeller University, 1230 York Avenue, New York, New York 10065, USA.
e-mail: shaham@rockefeller.edu

doi:10.1038/nrn2740
Published online 23 December 2009

1. Kandel, E. R. & Siegelbaum, S. A. in *Principles of Neural Science* (eds Kandel, E. R., Schwartz, J. H. & Jessell, T. M.) 175–186 (McGraw-Hill, 2000).
2. Spacek, J. Three-dimensional analysis of dendritic spines. III. Glial sheath. *Anat. Embryol. (Berl.)* **171**, 245–252 (1985).
3. Ventura, R. & Harris, K. M. Three-dimensional relationships between hippocampal synapses and astrocytes. *J. Neurosci.* **19**, 6897–6906 (1999).
4. Shaham, S. Glia-neuron interactions in nervous system function and development. *Curr. Top. Dev. Biol.* **69**, 39–66 (2005).
5. Benton, R., Vannice, K. S., Gomez-Diaz, C. & Vosshall, L. B. Variant ionotropic glutamate receptors as chemosensory receptors in *Drosophila*. *Cell* **136**, 149–162 (2009).
6. Mayer, M. L. & Armstrong, N. Structure and function of glutamate receptor ion channels. *Annu. Rev. Physiol.* **66**, 161–181 (2004).
7. Mayer, M. L. Glutamate receptors at atomic resolution. *Nature* **440**, 456–462 (2006).
8. Bargmann, C. I. & Horvitz, H. R. Chemosensory neurons with overlapping functions direct chemotaxis to multiple chemicals in *C. elegans*. *Neuron* **7**, 729–742 (1991).
9. Nelson, G. *et al.* An amino-acid taste receptor. *Nature* **416**, 199–202 (2002).
10. Alioto, T. S. & Ngai, J. The repertoire of olfactory C family G protein-coupled receptors in zebrafish: candidate chemosensory receptors for amino acids. *BMC Genomics* **7**, 309 (2006).
11. Chandrashekar, J., Hoon, M. A., Ryba, N. J. & Zuker, C. S. The receptors and cells for mammalian taste. *Nature* **444**, 288–294 (2006).
12. Schwartz, J. H. in *Principles of Neural Science* (eds Kandel, E. R., Schwartz, J. H. & Jessell, T. M.) 280–297 (McGraw-Hill, 2000).
13. Yassin, L. *et al.* Characterization of the deg-3/des-2 receptor: a nicotinic acetylcholine receptor that mutates to cause neuronal degeneration. *Mol. Cell. Neurosci.* **17**, 589–599 (2001).
14. Alberts, B. *et al.* in *Molecular Biology of the Cell* 5th edn (eds Alberts, B. *et al.*) 619–620 (Garland Science, 2008).
15. Sambongi, Y. *et al. Caenorhabditis elegans* senses protons through amphid chemosensory neurons: proton signals elicit avoidance behavior. *Neuroreport* **11**, 2229–2232 (2000).
16. Beg, A. A., Ernstrom, G. G., Nix, P., Davis, M. W. & Jorgensen, E. M. Protons act as a transmitter for muscle contraction in *C. elegans*. *Cell* **132**, 149–160 (2008).
17. Crump, J. G., Zhen, M., Jin, Y. & Bargmann, C. I. The SAD-1 kinase regulates presynaptic vesicle clustering and axon termination. *Neuron* **29**, 115–129 (2001).
18. Hung., W., Hwang, C., Po, M. D. & Zhen, M. Neuronal polarity is regulated by a direct interaction between a scaffolding protein, Neurabin, and a presynaptic SAD-1 kinase in *Caenorhabditis elegans*. *Development* **134**, 237–249 (2007).
19. Dwyer, N. D., Adler, C. E., Crump, J. G., L'Etoile, N. D. & Bargmann, C. I. Polarized dendritic transport and the AP-1 mu1 clathrin adaptor UNC-101 localize odorant receptors to olfactory cilia. *Neuron* **31**, 277–287 (2001).
20. Margeta, M. A., Wang, G. J. & Shen, K. Clathrin adaptor AP-1 complex excludes multiple postsynaptic receptors from axons in *C. elegans*. *Proc. Natl Acad. Sci. USA* **106**, 1632–1637 (2009).
21. Satoh, A. K., O'Tousa, J. E., Ozaki, K. & Ready, D. F. Rab11 mediates post-Golgi trafficking of rhodopsin to the photosensitive apical membrane of *Drosophila* photoreceptors. *Development* **132**, 1487–1497 (2005).
22. Brown, T. C., Correia, S. S., Petrok, C. N. & Esteban, J. A. Functional compartmentalization of endosomal trafficking for the synaptic delivery of AMPA receptors during long-term potentiation. *J. Neurosci.* **27**, 13311–13315 (2007).
23. Rosenbaum, J. L. & Carlson, K. Cilia regeneration in *Tetrahymena* and its inhibition by colchicine. *J. Cell Biol.* **40**, 415–425 (1969).
24. Matus, A., Ackermann, M., Pehling, G., Byers, H. R. & Fujiwara, K. High actin concentrations in brain dendritic spines and postsynaptic densities. *Proc. Natl Acad. Sci. USA* **79**, 7590–7594 (1982).
25. Sekerkova, G., Zheng, L., Loomis, P. A., Mugnaini, E. & Bartles, J. R. Espins and the actin cytoskeleton of hair cell stereocilia and sensory cell microvilli. *Cell. Mol. Life Sci.* **63**, 2329–2341 (2006).
26. Sekerkova, G. *et al.* Espins are multifunctional actin cytoskeletal regulatory proteins in the microvilli of chemosensory and mechanosensory cells. *J. Neurosci.* **24**, 5445–5456 (2004).
27. Flock, A. & Duvall, A. J. The ultrastructure of the kinocilium of the sensory cells in the inner ear and lateral line organs. *J. Cell Biol.* **25**, 1–8 (1965).
28. Flock, A. & Cheung, H. C. Actin filaments in sensory hairs of inner ear receptor cells. *J. Cell Biol.* **75**, 339–343 (1977).
29. Perkins, L. A., Hedgecock, E. M., Thomson, J. N. & Culotti, J. G. Mutant sensory cilia in the nematode *Caenorhabditis elegans*. *Dev. Biol.* **117**, 456–487 (1986).
30. Ward, S., Thomson, N., White, J. G. & Brenner, S. Electron microscopical reconstruction of the anterior sensory anatomy of the nematode *Caenorhabditis elegans*. *J. Comp. Neurol.* **160**, 313–337 (1975).
31. Satterlee, J. S. *et al.* Specification of thermosensory neuron fate in *C. elegans* requires *ttx-1*, a homolog of *otd/Otx*. *Neuron* **31**, 943–956 (2001).
32. Bacaj, T., Tevlin, M., Lu, Y. & Shaham, S. Glia are essential for sensory organ function in *C. elegans*. *Science* **322**, 744–747 (2008).
33. Jaworski, J. *et al.* Dynamic microtubules regulate dendritic spine morphology and synaptic plasticity. *Neuron* **61**, 85–100 (2009).
34. Nimchinsky, E. A., Sabatini, B. L. & Svoboda, K. Structure and function of dendritic spines. *Annu. Rev. Physiol.* **64**, 313–353 (2002).
35. Yasumatsu, N., Matsuzaki, M., Miyazaki, T., Noguchi, J. & Kasai, H. Principles of long-term dynamics of dendritic spines. *J. Neurosci.* **28**, 13592–13608 (2008).
36. McEwen, B. S. & Milner, T. A. Hippocampal formation: shedding light on the influence of sex and stress on the brain. *Brain Res. Rev.* **55**, 343–355 (2007).
37. Li, C. *et al.* Estrogen alters hippocampal dendritic spine shape and enhances synaptic protein immunoreactivity and spatial memory in female mice. *Proc. Natl Acad. Sci. USA* **101**, 2185–2190 (2004).
38. Mukhopadhyay, S., Lu, Y., Shaham, S. & Sengupta, P. Sensory signaling-dependent remodeling of olfactory cilia architecture in *C. elegans*. *Dev. Cell* **14**, 762–774 (2008).
39. Albert, P. S. & Riddle, D. L. Developmental alterations in sensory neuroanatomy of the *Caenorhabditis elegans* dauer larva. *J. Comp. Neurol.* **219**, 461–481 (1983).
40. Swoboda, P., Adler, H. T. & Thomas, J. H. The RFX-type transcription factor DAF-19 regulates sensory neuron cilium formation in *C. elegans*. *Mol. Cell* **5**, 411–421 (2000).
41. Senti, G. & Swoboda, P. Distinct isoforms of the RFX transcription factor DAF-19 regulate ciliogenesis and maintenance of synaptic activity. *Mol. Biol. Cell* **19**, 5517–5528 (2008).
42. Siegelbaum, S. A., Schwartz, J. H. & Kandel, E. R. in *Principles of Neural Science* (eds Kandel, E. R., Schwartz, J. H. & Jessell, T. M.) 229–252 (McGraw-Hill, 2000).
43. Buck, L. & Axel, R. A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. *Cell* **65**, 175–187 (1991).
44. Troemel, E. R., Chou, J. H., Dwyer, N. D., Colbert, H. A. & Bargmann, C. I. Divergent seven transmembrane receptors are candidate chemosensory receptors in *C. elegans*. *Cell* **83**, 207–218 (1995).
45. Palczewski, K. *et al.* Crystal structure of rhodopsin: a G protein-coupled receptor. *Science* **289**, 739–745 (2000).
46. Kim, E. & Sheng, M. PDZ domain proteins of synapses. *Nature Rev. Neurosci.* **5**, 771–781 (2004).
47. Tsunoda, S. *et al.* A multivalent PDZ-domain protein assembles signalling complexes in a G-protein-coupled cascade. *Nature* **388**, 243–249 (1997).
48. Li, Z., Benard, O. & Margolskee, R. F. Ggamma13 interacts with PDZ domain-containing proteins. *J. Biol. Chem.* **281**, 11066–11073 (2006).
49. Heiman, M. G. & Shaham, S. Ancestral roles of glia suggested by the nervous system of *Caenorhabditis elegans*. *Neuron Glia Biol.* **3**, 55–61 (2007).
50. Peters, A., Palay, S. L. & Webster, H. D. in *The Fine Structure of the Nervous System* 273–311 (Oxford Univ. Press, 1991).
51. Todd, K. J. & Robitaille, R. Neuron-glia interactions at the neuromuscular synapse. *Novartis Found. Symp.* **276**, 222–229; discussion 229–237, 275–281 (2006).
52. Finnemann, S. C. Focal adhesion kinase signaling promotes phagocytosis of integrin-bound photoreceptors. *EMBO J.* **22**, 4143–4154 (2003).
53. Suzuki, Y., Takeda, M. & Farbman, A. I. Supporting cells as phagocytes in the olfactory epithelium after bulbectomy. *J. Comp. Neurol.* **376**, 509–517 (1996).
54. Hansel, D. E., Eipper, B. A. & Ronnett, G. V. Neuropeptide Y functions as a neuroproliferative factor. *Nature* **410**, 940–944 (2001).
55. Nenov, A. P., Chen, C. & Bobbin, R. P. Outward rectifying potassium currents are the dominant voltage activated currents present in Deiters' cells. *Hear. Res.* **123**, 168–182 (1998).
56. Rio, C., Dikkes, P., Liberman, M. C. & Corfas, G. Glial fibrillary acidic protein expression and promoter activity in the inner ear of developing and adult mice. *J. Comp. Neurol.* **442**, 156–162 (2002).
57. Brechbuhl, J., Klaey, M. & Broillet, M. C. Grueneberg ganglion cells mediate alarm pheromone detection in mice. *Science* **321**, 1092–1095 (2008).
58. Mamasuew, K., Breer, H. & Fleischer, J. Grueneberg ganglion neurons respond to cool ambient temperatures. *Eur. J. Neurosci.* **28**, 1775–1785 (2008).
59. Smit, A. B. *et al.* A glia-derived acetylcholine-binding protein that modulates synaptic transmission. *Nature* **411**, 261–268 (2001).
60. Suh, J. & Jackson, F. R. *Drosophila* ebony activity is required in glia for the circadian regulation of locomotor activity. *Neuron* **55**, 435–447 (2007).
61. Christopherson, K. S. *et al.* Thrombospondins are astrocyte-secreted proteins that promote CNS synaptogenesis. *Cell* **120**, 421–433 (2005).
62. Yoshimura, S., Murray, J. I., Lu, Y., Waterston, R. H. & Shaham, S. *mls-2* and *vab-3* control glia development, *hlh-17*/Olig expression and glia-dependent neurite extension in *C. elegans*. *Development* **135**, 2263–2275 (2008).
63. White, J. G., Southgate, E., Thomson, J. N. & Brenner, S. The structure of the nervous system of the nematode *Caenorhabditis elegans*. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **314**, 1–340 (1986).
64. Westfall, J. A., Wilson, J. D., Rogers, R. A. & Kinnamon, J. C. Multifunctional features of a gastrodermal sensory cell in hydra: three-dimensional study. *J. Neurocytol.* **20**, 251–261 (1991).
65. Sakarya, O. *et al.* A post-synaptic scaffold at the origin of the animal kingdom. *PLoS ONE* **2**, e506 (2007).
66. Leys, S. P. & Degnan, B. M. Cytological basis of photoresponsive behavior in a sponge larva. *Biol. Bull.* **201**, 323–338 (2001).
67. Shah, A. S., Ben-Shahar, Y., Moninger, T. O., Kline, J. N. & Welsh, M. J. Motile cilia of human airway epithelia are chemosensory. *Science* **325**, 1131–1134 (2009).
68. L'Etoile, N. D. *et al.* The cyclic GMP-dependent protein kinase EGL-4 regulates olfactory adaptation in *C. elegans*. *Neuron* **36**, 1079–1089 (2002).
69. Kaye, J. A., Rose, N. C., Goldsworthy, B., Goga, A. & L'Etoile, N. D. A 3'UTR pumilio-binding element directs translational activation in olfactory sensory neurons. *Neuron* **61**, 57–70 (2009).
70. O'Halloran, D. M., Altshuler-Keylin, S., Lee, J. I. & L'Etoile, N. D. Regulators of AWC mediated olfactory plasticity in *Caenorhabditis elegans*. *PLoS Genet.* (in the press).
71. Bliss, T. V. & Lomo, T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J. Physiol.* **232**, 331–356 (1973).
72. Slack, J. R. & Pockett, S. Cyclic AMP induces long-term increase in synaptic efficacy in CA1 region of rat hippocampus. *Neurosci. Lett.* **130**, 69–72 (1991).
73. Thompson, K. R. *et al.* Synapse to nucleus signaling during long-term synaptic plasticity; a role for the classical active nuclear import pathway. *Neuron* **44**, 997–1009 (2004).

74. Mauch, D. H. *et al.* CNS synaptogenesis promoted by glia-derived cholesterol. *Science* **294**, 1354–1357 (2001).
75. Fuentes-Medel, Y. *et al.* Glia and muscle sculpt neuromuscular arbors by engulfing destabilized synaptic boutons and shed presynaptic debris. *PLoS Biol.* **7**, e1000184 (2009).
76. Colon-Ramos, D. A., Margeta, M. A. & Shen, K. Glia promote local synaptogenesis through UNC-6 (netrin) signaling in *C. elegans*. *Science* **318**, 103–106 (2007).
77. Murai, K. K., Nguyen, L. N., Irie, F., Yamaguchi, Y. & Pasquale, E. B. Control of hippocampal dendritic spine morphology through ephrin-A3/EphA4 signaling. *Nature Neurosci.* **6**, 153–160 (2003).
78. Rothstein, J. D. *et al.* Knockout of glutamate transporters reveals a major role for astroglial transport in excitotoxicity and clearance of glutamate. *Neuron* **16**, 675–686 (1996).
79. Adams, R. H. *et al.* Gene structure and glial expression of the glycine transporter GlyT1 in embryonic and adult rodents. *J. Neurosci.* **15**, 2524–2532 (1995).
80. Minelli, A., DeBiasi, S., Brecha, N. C., Zuccarello, L. V. & Conti, F. GAT-3, a high-affinity GABA plasma membrane transporter, is localized to astrocytic processes, and it is not confined to the vicinity of GABAergic synapses in the cerebral cortex. *J. Neurosci.* **16**, 6255–6264 (1996).
81. Araque, A., Parpura, V., Sanzgiri, R. P. & Haydon, P. G. Glutamate-dependent astrocyte modulation of synaptic transmission between cultured hippocampal neurons. *Eur. J. Neurosci.* **10**, 2129–2142 (1998).
82. Heumann, R., Villegas, J. & Herzfeld, D. W. Acetylcholine synthesis in the Schwann cell and axon in the giant nerve fiber of the squid. *J. Neurochem.* **36**, 765–768 (1981).
83. Minchin, M. C. & Iversen, L. L. Release of (^{3}H)gamma-aminobutyric acid from glial cells in rat dorsal root ganglia. *J. Neurochem.* **23**, 533–540 (1974).
84. Newman, E. A. Glial cell inhibition of neurons by release of ATP. *J. Neurosci.* **23**, 1659–1666 (2003).
85. Oliet, S. H. & Mothet, J. P. Regulation of *N*-methyl-D-aspartate receptors by astrocytic D-serine. *Neuroscience* **158**, 275–283 (2009).

Acknowledgements
I would like to thank J. Darnell, M. Heiman, M. Nedergaard and L. Vosshall for comments and discussions of the ideas presented here and R. Benton and Y. Lu for sharing images. This work was supported in part by US National Institutes of Health grant R01NS064273.

Competing interests statement
The author declares no competing financial interests.

DATABASES
Entrez Gene: http://www.ncbi.nlm.nih.gov/gene
daf-19 | *ttx-1*
UniProtKB: http://www.uniprot.org
EB3 | Ggamma13 | neurabin | p140Cap | PSD95 | RAB11 | SAD1 | Veli-2

FURTHER INFORMATION
Shai Shaham's homepage: http://shahamlab.rockefeller.edu

ALL LINKS ARE ACTIVE IN THE ONLINE PDF

ONLINE CORRESPONDENCE

Nature Reviews Neuroscience publishes items of correspondence online. Such contributions are published at the discretion of the Editors and can be subject to peer review. Correspondence should be no longer than 500 words with up to 15 references and should represent a scholarly attempt to comment on a specific Review or Perspective article that has been published in the journal. To view correspondence, please go to our homepage at: http://www.nature.com/nrn and follow the link from the current table of contents. To cite correspondence, please use its doi number.

The following correspondence has recently been published:

Overnight alchemy: sleep-dependent memory evolution
Matthew P. Walker & Robert Stickgold
doi:10.1038/nrn2762-c1

Title [Au: please provide title]
Susanne Diekelmann & Jan Born
doi:10.1038/nrn2762-c2

This correspondence relates to the article:

The memory function of sleep
Susanne Diekelmann & Jan Born
Nature Reviews Neuroscience **11**, 114-126 (2010)

CORRIGENDUM

CART peptides: regulators of body weight, reward and other functions

G. Rogge, D. Jones, G. W. Hubert, Y. Lin and M. J. Kuhar

Nature Reviews Neuroscience **9**, 747–758 (2008)

In figure 4a of the article, the doses of the bilateral CART (cocaine- and amphetamine-regulated transcript) peptide infusions were incorrectly given in milligrams. In both the figure and the legend, the doses should be 0.0, 1.0 or 2.5 μg per side.