their electrical characteristics will scale predictably. For example, at the nanometre scale, strong electronic interactions between the molecules and the metal electrodes, a disordered arrangement of molecules in the devices, the presence of contaminants and electric fields that increase in strength as the dimensions decrease could all alter the electrical characteristics in a non-trivial manner[6,7].

Furthermore, molecular memristors alone do not constitute the complete set of circuits required for a computing processor. CMOS transistors will be needed to regulate voltage and interface with external systems, for example. Therefore, molecular memristors must eventually be integrated with CMOS circuitry and will need to be compatible with standard semiconductor fabrication processes.

It is not yet clear how efficiently molecular devices will work together as required by a general-purpose processor. Standard tools for electronic design automation that are used in software compilers and chip design will all need substantial adjustments to accommodate the proposed computing paradigm. The combined design of computing algorithms, architectures and devices will enable the full potential of a molecular-memristor processor to be understood. Despite the research challenges, molecular-memristor computing offers a promising path to highly efficient, scalable, general-purpose information-processing systems.

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1. Goswami, S. *et al. Nature* **597**, 51–56 (2021).
2. Strukov, D. B., Snider, G. S., Stewart, D. R. & Williams, R. S. *Nature* **453**, 80–83 (2008).
3. Balatti, S., Larentis, S., Gilmer, D. C. & Ielmini, D. *Adv. Mater.* **25**, 1474–1478 (2013).
4. Mickel, P. R., Lohn, A. J., James, C. D. & Marinella, M. J. *Adv. Mater.* **26**, 4486–4490 (2014).
5. Zhirnov, V. V. & Cavin, R. K. *Nature Mater.* **5**, 11–12 (2006).
6. van der Molen, S. J. & Liljeroth, P. *J. Phys. Condens. Matter* **22**, 133001 (2010).
7. Troisi, A., Orlandi, G. & Anthony, J. E. *Chem. Mater.* **17**, 5024–5031 (2005).

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Structural biology

A receptor that lets insects sense scents

Emily R. Liman

In insects, odorant receptor proteins form membrane ion channels that open on binding to an odorant molecule. The structures of an inactive and an active channel lend insights into how insects detect and distinguish between odours. **See p.126**

As we apply insect repellents in an effort to thwart insect-borne diseases, we might stop to wonder how these substances work and why they are not more effective. DEET, the compound most commonly used in insect repellents, is thought to broadly activate insects' odorant receptor proteins, scrambling the olfactory code the insects use for seeking a host[1]. But how DEET or natural odorant molecules bind to and affect the activity of insect odorant receptors has not been clear. Del Mármol *et al.*[2] (page 126) report the structure of an insect odorant receptor in association with DEET or with the odorant eugenol, thereby providing key insights into how odorants bind to the receptor and how the structure of the activated receptor subsequently changes.

Olfactory systems in different animals have evolved to accomplish highly specialized tasks. A fruitfly homes in on rotting fruit and a mosquito on its host, whereas humans can discriminate between a wide range of food-related scents. Vertebrates and invertebrates alike detect and distinguish between vast numbers of volatile chemicals using a large set of odorant receptors. In many cases, receptor–odorant binding is promiscuous: that is, a single odorant might activate multiple receptors, and each receptor might be activated by multiple odorants. Olfactory neuronal cells each express one type of odorant receptor. Thus, each odorant can activate a different (but sometimes overlapping) set of neurons, creating a combinatorial code to be deciphered by the nervous system[3–5].

General principles for odorant coding in fruitflies and humans are remarkably similar. For example, in both species, projections of olfactory neurons expressing the same receptor converge at hub-like structures called glomeruli. However, the receptor proteins in insects and vertebrates could not be more dissimilar. Vertebrate odorant receptors are members of the G-protein-coupled family of receptors[6], whereas insect receptors are ion channels that open on binding to an odorant molecule[7–10].

This much has been known for decades, but what was not known was how a single odorant receptor could respond to such a large array of structurally diverse molecules. The lock-and-key model of receptor–ligand binding, first espoused by Emil Fischer in 1894, posits that the shapes of a ligand molecule and its binding site in a receptor complement each other exactly[11]. But this is woefully inadequate for explaining receptor promiscuity[12]. The structure of an odorant receptor in complex with diverse odorants was needed to shed light on this phenomenon.

To achieve this, del Mármol *et al.* focused on insect odorant receptors. Most such receptors are assembled from a combination of different subunits (that is, as hetero-multimers), with all receptors containing one particular subunit, Orco, and another, variable subunit that confers ligand specificity[13]. Previously, single-particle cryo-electron microscopy (cryo-EM) was used to solve the structure of a receptor comprising four Orco subunits[14], elucidating the basic architecture of this homo-tetrameric channel. But Orco does not contain a ligand-binding site for the receptor, and so the binding site was not resolved. To solve the structure of a complete insect odorant receptor, while avoiding difficulties associated with resolving the structure of hetero-multimeric proteins, del Mármol *et al.* focused on an insect odorant receptor that can assemble as a functional homomeric protein in the absence of Orco.

Heteromeric proteins consisting of similar subunits typically arise through a gene duplication that occurs in the process of evolution. Thus, del Mármol *et al.* reasoned that a functional homomeric odorant receptor would be found in more evolutionarily ancient organisms, and focused on the jumping bristletail *Machilis hrabei*, a relative of silverfish. In jumping bristletails, the receptor repertoire consists of combinations of just five subunits (*Mh*OR1–5), none of which is directly related to Orco[15]. Each *Mh*OR5 subunit contains nine

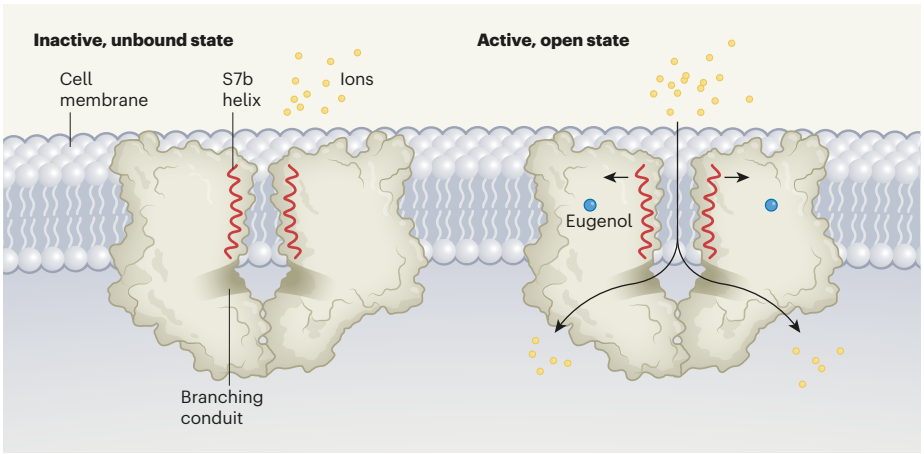

Figure 1 | The closed and open states of an insect odorant receptor. In insects, receptors on olfactory cells that detect odorant molecules are ion channels made up of four protein subunits. Del Mármol *et al.*[2] used cryo-electron microscopy to resolve the structure of an odorant receptor from the jumping bristletail (*Machilis hrabei*) in its inactive, unbound (apo) state and its active, open state. Each of the four identical subunits contributes to a central ion-permeation pathway; two subunits are shown in each case here. When bound to an odorant such as eugenol, the S7b helix of each of the subunits rotates slightly, widening the pore of the channel near the outer surface of the cell membrane. Ions travel through to a large vestibule, before passing through one of four laterally branching conduits into the cell.

α-helices, with six of these spanning the width of the cell membrane (S1–S6), two others (S0 and S7b) partially spanning the membrane and the last (S7a) situated inside the membrane.

The authors tested how channels made from four *Mh*OR5 or four *Mh*OR1 subunits responded to different ligands. They found that *Mh*OR5 channels are broadly tuned, responding to more than 60% of the chemicals they tested (including eugenol and DEET), whereas MhOR1 channels are more selective.

The authors then used cryo-EM to solve the structures of an *Mh*OR5 channel in the unliganded state (known as the apo state), or when bound to DEET or to eugenol (Fig. 1). Overall, the structures they resolved are similar to that of the Orco homomer.

The structures reveal that, when the channel is activated and open, positively charged ions follow a pathway from a large outer vestibule into a single, membrane-spanning conduit that is lined by amino-acid residues from the S7b α-helices of each of the four subunits. On the intracellular side of the receptor, four conduits diverge laterally from the centre, to complete the ions' pathway into the cell. In the apo state, the narrowest portion of the pathway, measuring 5.3 ångströms in diameter, is found where a valine amino-acid residue in the S7b helix projects into the central lumen, creating a hydrophobic 'plug' that restricts ion conduction.

A comparison of apo and ligand-bound states reveals two key architectural features that might explain how the odorant receptor channels, in general, are able to respond to broad arrays of ligands. First, the transition of the channel from a closed to an open state involves only a slight rotation of the S7b helix, which widens the pore and moves a polar residue into the ion-conduction pathway. This movement is likely to require very little energy compared with, for example, the movement of the S4 region during the opening of a voltage-gated ion channel[16]. Such a low energy requirement for opening might be the key to the ligand promiscuity of the odorant receptor: even the binding of ligands that have low affinity for the receptor can lead to this rearrangement.

Equally important is the nature of the ligand-binding site, which seems to be unusually flexible and able to accommodate ligands of varying chemical composition in multiple orientations. This ligand-binding pocket, located deep within the loose bundle formed by the transmembrane parts of the S2, S3, S4 and S6 helices, is lined by mostly large aromatic and hydrophobic residues that form non-polar interactions with the ligand. This contrasts with the stricter geometric constraints that are imposed by the hydrogen bonds (which are extremely polar) observed in the binding sites of many other types of receptor.

Furthermore, the binding site of the *Mh*OR5 receptor seems to undergo rearrangements to accommodate ligands of different sizes and shapes. Subtle mutations in the pocket change ligand specificity, essentially retuning the receptors. This provides a mechanism by which evolution could have given rise to the large number of receptors with different ligand specificities that are observed in extant insect species.

At long last, 30 years after the discovery of vertebrate odorant receptors[6], we have the structure of an odorant receptor in complex with its ligand. But, much as this advance answers age-old questions, it also raises new ones. For example, the structures of neither the apo nor the ligand-bound receptors show a pathway for odorants to access the ligand-binding pocket. One possibility is that the channel 'breathes', transiently opening a pathway through which odorants can get to this site and thereby lock the channel in an open conformation. Defining the odorant-access pathway through studies of the structure and function of the receptor might provide further insights into receptor specificity.

This and previous studies (for example, ref. 9) also raise the question of how a system in which receptors are active in the absence of a ligand (albeit at a low level) can distinguish between the signal from ligand-bound receptors and the noise of active, but ligand-free, receptors. One possibility is that the olfactory system can tolerate a certain amount of noise, because it can continue to collect and integrate new information over time: for example, as an insect nears an odour source, it might use new, higher-quality olfactory information to correct its course. Another possibility is that the organization of the olfactory system into glomeruli that pool information from many neurons effectively filters out activity of single errant neurons. Analyses of the processing of odorant signals in glomeruli and by the central nervous system might be needed to answer these questions.

Finally, one wonders whether these findings can be generalized to describe vertebrate G-protein-coupled odorant receptors. Like their insect counterparts, vertebrate odorant receptors bind to odorants mainly through non-polar and weakly polar interactions[17]. Might they also be endowed with a flexible ligand-binding pocket and low energy barrier for engaging downstream signalling, which together enable them to respond to various relatively low-affinity ligands? Undoubtedly, the work of del Mármol *et al.* and future studies will lead to the development of designer ligands for odorant receptors, and perhaps even, someday, to a substitute for DEET.

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1. Pellegrino, M., Steinbach, N., Stensmyr, M. C., Hansson, B. S. & Vosshall, L. B. *Nature* **478**, 511–514 (2011).
2. del Mármol, J., Yedlin, M. A. & Ruta, V. *Nature* **597**, 126–131 (2021).
3. Nara, K., Saraiva, L. R., Ye, X. & Buck, L. B. *J. Neurosci.* **31**, 9179–9191 (2011).
4. Araneda, R. C., Kini, A. D. & Firestein, S. *Nature Neurosci.* **3**, 1248–1255 (2000).
5 Hallem, E. A., Ho, M. G. & Carlson, J. R. *Cell* **117**, 965–979 (2004).
6. Buck, L. & Axel, R. *Cell* **65**, 175–187 (1991).
7. Clyne, P. J. *et al. Neuron* **22**, 327–338 (1999).
8. Vosshall, L. B., Amrein, H., Morozov, P. S., Rzhetsky, A. &

Axel, R. *Cell* **96**, 725–736 (1999).
9. Sato, K. *et al. Nature* **452**, 1002–1006 (2008).
10. Wicher, D. *et al. Nature* **452**, 1007–1011 (2008).
11. Fischer, E. *Ber. Deutsch. Chem. Ges. Berlin* **27,** 2985–2993 (1894).
12. Tripathi, A. & Bankaitis, V. A. *J. Mol. Med. Clin. Appl.* **2**, https://dx.doi.org/10.16966/2575-0305.106 (2017).
13. Larsson, M. C. *et al. Neuron* **43**, 703–714 (2004).
14. Butterwick, J. A. *et al. Nature* **560**, 447–452 (2018).
15. Brand, P. *et al. eLife* **7**, e38340 (2018).
16. Catterall, W. A., Wisedchaisri, G. & Zheng, N. *Nature Chem. Biol.* **16**, 1314–1320 (2020).
17. Katada, S., Hirokawa, T., Oka, Y., Suwa, M. & Touhara, K. *J. Neurosci.* **25**, 1806–1815 (2005).

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Neuroscience

A signal to synchronize thought with metabolism

Manfred Hallschmid & Jan Born

In a brain structure called the hippocampus, sharp wave-ripples — oscillatory hallmarks of an 'offline' mode of cognitive processing — have been found to predict dips in glucose concentrations in the body. **See p.82**

To regulate adaptive behaviour, the brain relies on a continuous flow of cognitive and memory-related processes that require a constant energy supply. Weighing around 1,200 grams in women and 1,300 grams in men, on average, the brain consumes around 90 grams, or 340 kilocalories' worth, of glucose per day, accounting for around half of the body's glucose demand[1,2]. The tight integration of metabolic and cognition-related signals might aid the matching of the brain's energy supply to its energy needs, by optimizing foraging behaviour and efforts to limit energy expenditure. The synchronization of glucose supply with brain activity has so far been considered a function of a structure called the hypothalamus, at the base of the brain. On page 82, Tingley *et al.*[3] provide evidence in rats for the role of another brain region, called the hippocampus, which is typically implicated in memory and navigation, in this equation (Fig. 1).

The hippocampus receives many types of sensory and metabolic information, and projections from neuronal cells in the hippocampus extend to various parts of the brain, including the hypothalamus. Thus, the hippocampus might indeed represent a hub in which metabolic signals are integrated with cognitive processes[3]. To examine this possibility, Tingley and colleagues recorded oscillatory patterns called sharp wave-ripples (SPW-Rs), reflecting changes in electrical potential across the cell membranes of neuronal-cell ensembles in the hippocampi of rats. They did this while using a sensor inserted under the skin of the animals' backs to continuously measure glucose levels in the interstitial fluid surrounding the cells there.

SPW-Rs are composed of a sharp wave, arising from neurons in the CA3 region of the hippocampus, that brings about a fast but localized network oscillation — the ripple — in the CA1 and connected regions. Crucially, SPW-Rs are associated with synchronous bursts of neuronal firing, and represent a hallmark of cognitive, specifically memory-related, processing of experience[4].

The authors demonstrated that clustered SPW-Rs recorded in a part of the hippocampus called the dorsal CA1 are followed by a distinct drop in peripheral glucose concentrations around 10 minutes later. Although the rate of SPW-Rs, which averaged almost 10 per minute, varied considerably over a 24-hour cycle, the authors show that a reduction in glucose concentrations of about 0.33 milligrams per decilitre emerged per SPW-R. SPW-Rs that had a large amplitude but short duration and were clustered together in time predicted the most-pronounced drops in glucose.

This striking observation suggests a previously unknown role of SPW-Rs as a phase-resetting signal to control an animal's glucose levels. Certain aspects of this proposed role require some thought, including the timing of the observed glucose responses. The delay of roughly 10 minutes between SPW-Rs and the drop in glucose might be explained by factors such as the low speed of the diffusion of glucose into the interstitial space, and a technical delay that is inherent in an implanted sensor's glucose readout. Therefore, the coupling of the hippocampus and peripheral glucose levels through SPW-Rs might be even tighter.

Another aspect to be considered is the direction of change in glucose levels after SPW-Rs. These oscillatory patterns are associated with increased firing activity in the hippocampus,

From the archive

A look back at the life of Lawrence Bragg, and a call for London to erect a statue of Louis Pasteur.

50 years ago

Sir Lawrence Bragg, who died on July 1 aged 81, had the unique distinction of having himself created the science to which he devoted his life's work, and lived long enough to experience its revolutionary impact, first on inorganic chemistry and mineralogy, then on metallurgy, and finally on organic chemistry and biochemistry … Röntgen discovered X-rays when Bragg was five years old, and von Laue, Friedrich and Knipping demonstrated X-ray diffraction by crystals in the spring of 1912, when Bragg was taking his physics degree at Cambridge … By a remarkable feat of imaginative insight Bragg … reformulated von Laue's conditions for diffraction into what became known as Bragg's Law, which gives a direct relationship between the crystal structure and its diffraction pattern … If we think of Bragg as an artist and compare him to, say, Giotto, it is as though he had himself invented three dimensional representation, and then lived through all the styles of European painting from the Renaissance to the present day, to be finally confronted by computer art … To the present young generation Bragg was an avuncular figure who showed them that science can be fun. At the Royal Institution he instituted a series of physics lectures for sixth formers … Bragg's superb powers of combining simplicity with rigour, his enthusiasm, liveliness and charm of manner, and his beautiful demonstrations all conspired to make him one of the best lecturers on science that ever lived. **M. F. Perutz**

From *Nature* 3 September 1971

100 years ago

France is already preparing to celebrate … the centenary of the birth of Pasteur … If every Englishman and Englishwoman who has cause to be grateful to him and his followers would subscribe sixpence, we should obtain enough money for a lifesize golden image … It is one of our national disgraces that there is no memorial to him in London.

From *Nature* 1 September 1921