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NEUROSCIENCE

Current views on odour receptors

Alexander Chesler and Stuart Firestein

Insects possess refined olfactory systems that use specific receptors on their antennae. It emerges that these receptors not only detect odour molecules but, unexpectedly, can also act as ion channels.

All creatures sample their environment for chemicals that indicate the presence of food, mates, predators, dangers and attractions through mechanisms that were thought to be evolutionarily conserved from nematode worms to mammals. For example, in many organisms, odorant molecules bind to their receptors on the surface of neurons, initiating an intracellular signalling cascade. This ultimately results in the opening of ion channels conveying current, thereby completing the transformation of these chemical signals into electrical signals. It was thus assumed that the olfactory system of flies would function similarly. But when the fly odour receptor proteins were finally identified[1–3], a new riddle surfaced: what are the intermediary molecules that couple these receptors to the activation of ion channels in insect sensory neurons? Reporting in this issue, Sato *et al.*[4] and Wicher *et al.*[5] provide an answer to this question, but in doing so raise others that are just as puzzling.

To detect odours, vertebrates and worms use members of a large family of G-protein-coupled receptors (GPCRs), which thread through the cell membrane seven times. The initial identification of odorant receptors (ORs) in insects relied on the assumption that these organisms also detect odours through GPCRs. In 1999, three laboratories identified[1–3] a family of these 'seven-transmembrane' receptors whose expression in the antennae of the fruitfly *Drosophila melanogaster* turned out[6] to control the responses of individual olfactory neurons to chemical odorants.

But the first hint that insects detect odours differently from mammals came from analysis of the receptors' amino-acid sequences[1–3]. Although the vertebrate receptors are similar in sequence to other known GPCRs, the fly receptors are not. Moreover, unlike mammals, in which only one gene encoding a receptor is believed to be expressed in a given neuron, in fly sensory neurons at least one member of the receptor family Or83b is co-expressed with the insect odorant receptors. (Or83b is an essential co-receptor that does not bind to any known ligand, but is necessary for the intracellular transport and proper function of its companion receptor[7].) Finally, and perhaps most peculiarly, the insect receptors seem to lie in the membrane in the opposite configuration to GPCRs — that is, their amino terminus faces the cytoplasm and their carboxy terminus faces the outside[8].

The observations of Sato *et al.*[4] (page 1002) and Wicher *et al.*[5] (page 1007) may set things straight, albeit in an unexpected way. Both teams independently find that odour stimulation of multi-unit OR/Or83b complexes in cells grown in culture leads to inward cationic currents. Moreover, they show that the ionic conductance and permeability of the channels carrying these currents are similar to those of other known voltage-independent, non-selective channels for positive ions. Together, the authors' observations provide compelling evidence that, for odour detection, insects use an unusual strategy and an unusual receptor — the 'receptor' is in fact an ion channel. However, the two groups[4,5] have remarkably different mechanistic views of the sequence of events that occur from ligand binding to channel opening.

Through various experiments, Sato *et al.* rule out any role for G proteins. Instead, they conclude that the OR/Or83b complexes include an ion-channel function that is directly activated by odorant ligands. By contrast, Wicher and colleagues' data implicate a signalling molecule — the cyclic nucleotide cAMP — that is produced in response to G-protein-mediated signalling, which then activates the receptor/channel. These authors find that cAMP is generated in response to odours, and that modulators of G-protein signalling can affect OR/Or83b function. Most surprisingly, they also show that Or83b alone can form a cyclic-nucleotide-sensitive channel.

How can these contradictory findings be reconciled? One explanation might lie in the timescale of events that the two groups investigated. Sato *et al.* concerned themselves with the initial response that occurs within the first second or so after odour application, whereas Wicher *et al.* focused mainly on the cAMP-dependent responses that peak at between 30 and 60 seconds. So it could be that the opening of OR/Or83b complexes is regulated by both ligands and cyclic nucleotides, but on different timescales: odorants mediate fast detection by opening the channels, whereas cyclic nucleotides provide longer-lasting modulation. Although further work is needed to tease all this apart, the two studies add yet another unexpected twist to our knowledge of the seven-transmembrane receptor family: along with another GPCR channel, channelrhodopsin, and the structurally similar halorhodopsin ion pump[9,10], there is now an odour-activated channel receptor.

The coincidental arrival of these two papers and the subsequent review process raises an interesting set of editorial issues. We acted as a referee, and were somewhat involved in the process. Separately, each paper presents a convincing argument for a novel receptor-channel protein; taken together, they contain contradictory data that are difficult to reconcile. Of course, this is not the first time papers with contradictory views have been published. In the 1980s a controversy raged over the identity of the intermediate signalling molecule in photoreception — calcium or cGMP. No fewer than five papers appeared in *Nature* alone describing results that supported one or the other candidate, until a pivotal experiment[11] resolved the issue in favour of cGMP. Although journals, editors and reviewers have a responsibility to vet papers for accuracy and correctness, we must also recognize that, at its frontiers, science doesn't always produce unequivocal data. It is no less a responsibility to ensure that the literature accurately reflects what is known at the time. As George Bernard Shaw (paraphrasing Immanuel Kant) said in a toast to Albert Einstein: "Science is always wrong. It never solves a problem without creating ten more." Would we have it otherwise? ■

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