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concept

Ionotropic and metabotropic mechanisms in chemoreception: 'chance or design'?

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Chemosensory receptors convert an enormous diversity of chemical signals from the external world into a common language of electrical activity in the brain. Mammals and insects use several families of transmembrane receptor proteins to recognize distinct classes of volatile and non-volatile chemicals that are produced by conspecifics or other environmental sources. A comparison of the signalling mechanisms of mammalian and insect receptors has revealed an unexpected functional distinction: mammals rely almost exclusively on metabotropic ligand-binding receptors, which use second messenger signalling cascades to indirectly activate ion channels, whereas insects use ionotropic receptors, which are gated directly by chemical stimuli, thereby leading to neuronal depolarization. In this review, we consider possible reasons for this dichotomy, taking into account biophysical, cell biological, ecological and evolutionary influences on how information is extracted from chemosensory cues by these animal classes.

Keywords: olfaction; gustation; receptor; GPCR; ion channel

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See Glossary for abbreviations used in this article.

Introduction

Anyone who has extracted a drowning fly from a glass of wine, swatted a wasp from a pot of jam or stamped on an army of ants approaching a picnic basket will have a keen appreciation for the common attractiveness of a multitude of chemosensory cues to insects and mammals. Similarly, many poisonous compounds that are often found in plants trying to evade predation are aversive to both animal classes. Such parallels naturally reflect the basic need of organisms with a largely conserved cellular metabolism to identify nutritional food sources and avoid intoxication. Advances in our understanding of the neuroanatomical logic and physiological coding properties of insect and mammalian olfactory and gustatory systems—which are normally associated with the detection of volatile and non-volatile stimuli, respectively—have revealed important commonalities in how insects and mammals process and represent chemical signals in the brain. These similarities are suggestive either of the evolution of these chemosensory systems from those present in a common ancestral animal, or of their convergent shaping by the same selective constraints, defined by their role in mediating odour-evoked and taste-evoked behaviours (Ache & Young, 2005; Benton, 2009; Hildebrand & Shepherd, 1997; Scott, 2005; Strausfeld & Hildebrand, 1999; Su *et al*, 2009; Yarmolinsky *et al*, 2009).

However, recent investigations into the molecular mechanisms of chemosensory signalling have revealed an unexpected dichotomy: mammals (and vertebrates in general) almost exclusively use metabotropic chemosensory receptors—that is, the ligand-binding receptors indirectly activate ion channels through second messengers—whereas insects (and possibly all arthropods) might predominantly use ionotropic mechanisms, in which the primary chemosensory receptors are ligand-gated ion channels (Pellegrino & Nakagawa, 2009; Spehr & Munger, 2009; Touhara & Vosshall, 2009).

In mice, for example, five families of olfactory sensory receptors are now known: ORs and trace amine-associated receptors, which are expressed in olfactory sensory neurons (OSNs) in the main olfactory epithelium, and V1R, V2R and formyl peptide receptors, which are expressed in the vomeronasal organ—an accessory olfactory system believed to be dedicated mainly to pheromone recognition (Fig 1; Spehr & Munger, 2009; Touhara & Vosshall, 2009). These five families belong to the GPCR superfamily of seven transmembrane domain proteins that signal through the activation of heterotrimeric G proteins. Olfactory signal transduction has been best defined for ORs (Fig 2; Kleene, 2008), which are coupled to an olfactory G-protein subunit ($G\alpha_{olf}$). $G\alpha_{olf}$ activates adenylyl cyclase III, leading to cAMP production, which binds to and opens a multisubunit CNG. The influx of Ca^{2+} through this channel promotes the opening of a calcium-gated chloride channel—which is probably anoctamin 2 (Stephan *et al*, 2009)—and the combined effect of calcium influx and chloride efflux leads to OSN depolarization. The olfactory GPCR families are not slight variants of each other, but instead represent distinct and evolutionarily ancient clades that are discernible across vertebrates (Nei *et al*, 2008; Shi & Zhang, 2009). Furthermore, their expression in different subsets of olfactory neurons or organs and their responsiveness to specific classes of ligand imply that they fulfil distinct functions in odour perception (Fig 1; Spehr & Munger, 2009; Su *et al*, 2009; Touhara & Vosshall, 2009).

Most receptors underlying mammalian taste perception are also GPCRs, including the T1R family, which recognizes sweet and umami stimuli, and the T2Rs, which underlie bitter taste detection (Chandrashekar *et al*, 2006; Yarmolinsky *et al*, 2009). These families

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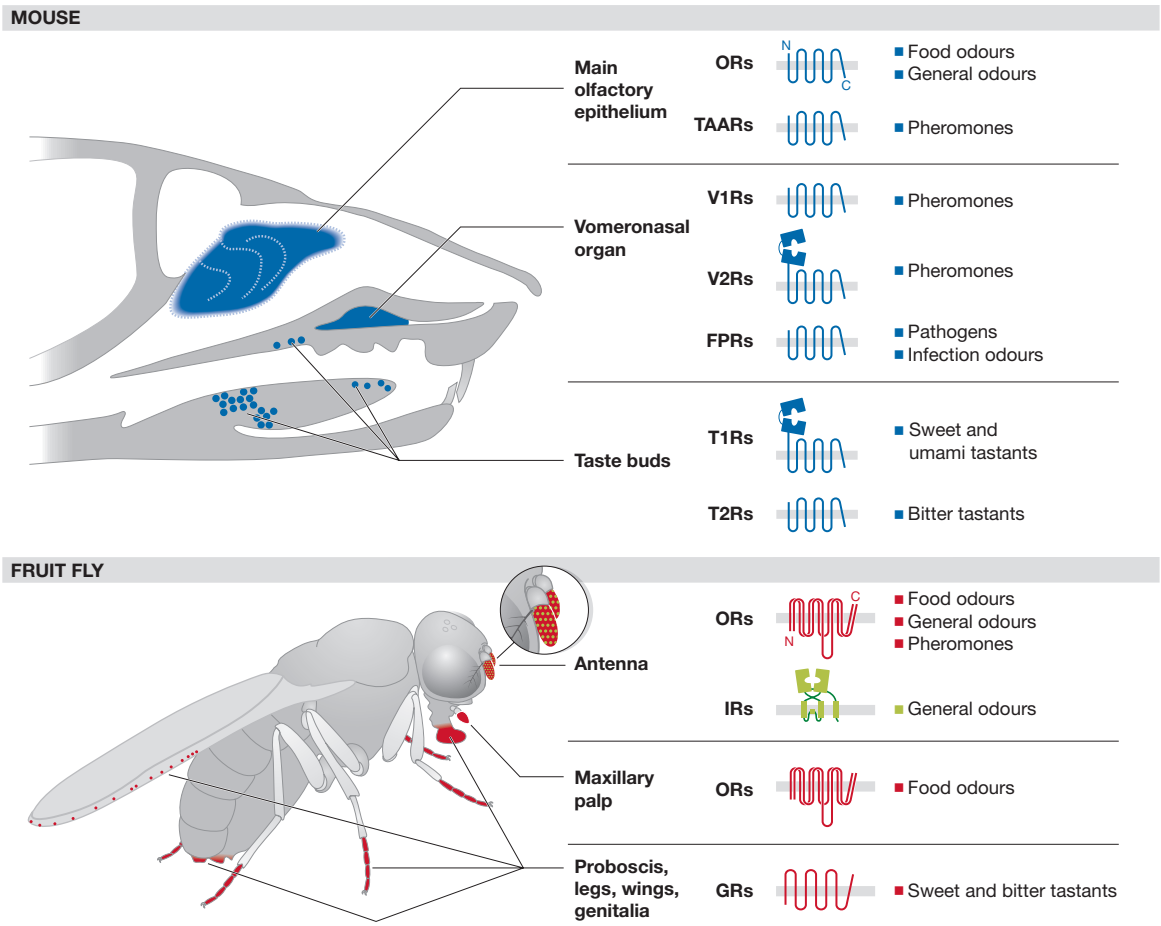

Fig 1 | The main chemosensory organs, receptors and putative ligands in the mouse and the fruit fly. The image of the mouse head was adapted from Matsunami & Amrein (2003). FPRs, formyl peptide receptors; GRs, gustatory receptors; IRs, ionotropic receptors; ORs, odorant receptors; T1Rs, taste receptors type 1; T2Rs, taste receptors type 2; TAARs, trace amine-associated receptors; V1Rs, vomeronasal receptors type 1; V2Rs, vomeronasal receptors type 2.

also define distinct subclassess of GPCR, although T1Rs are distantly related to V2Rs.

Insect chemosensory receptors have been best characterized at a molecular level in the fruit fly *Drosophila melanogaster* (Benton, 2008; Vosshall & Stocker, 2007). These proteins localize to the ciliated endings of sensory neuron dendrites, housed in porous cuticular hairs called sensilla, that cover the external surface of chemosensory organs (Fig 1). ORs are expressed in the olfactory organs, the antenna and maxillary palp, whereas GRs are expressed predominantly in the proboscis and various other contact chemosensors on the legs, wings and genitalia (Fig 1; Stocker, 1994). *Drosophila* ORs and GRs are related families of polytopic transmembrane proteins that appear to be largely arthropod-specific or—in the case of ORs—insect-specific (Penalva-Arana *et al*, 2009; Robertson *et al*, 2003). Although they are predicted to contain seven transmembrane domains, they are unrelated in sequence to GPCRs; structural analysis has shown they adopt a distinct membrane topology, with intracellular amino-termini, which is probably shared by GRs (Benton *et al*, 2006; Lundin *et al*, 2007). A functional analysis of ORs has provided compelling evidence that their primary transduction mechanism is ionotropic (Fig 2), and that a complex of a ligand-binding OR and the OR co-receptor OR83b—which is essential for subcellular localization and function (Benton *et al*, 2006; Larsson *et al*, 2004)—acts as an odour-gated ion channel (Sato *et al*, 2008; Smart *et al*, 2008; Wicher *et al*, 2008). Although the involvement of G proteins and second messengers downstream from insect ORs has been studied intensively over the past decade, their contribution to odour sensing remains unclear, and *in vivo* they might have a principally modulatory role. These issues have been discussed in detail elsewhere (Benton, 2008; Nakagawa & Vosshall, 2009; Pellegrino & Nakagawa, 2009; Ronderos & Smith, 2009). Little is known about how GRs transduce signals, but their homology to ORs makes it plausible that these receptors also function as ion channels.

Recently, a third family of *Drosophila* chemosensory receptors—the IRs—has been identified (Benton *et al*, 2009). IRs were named for their homology to iGluRs, a class of ligand-gated ion channels best characterized for their role in mediating synaptic transmission. Importantly, IRs contain divergent ligand-binding domains that lack glutamate-interacting residues. The conservation of the ion channel

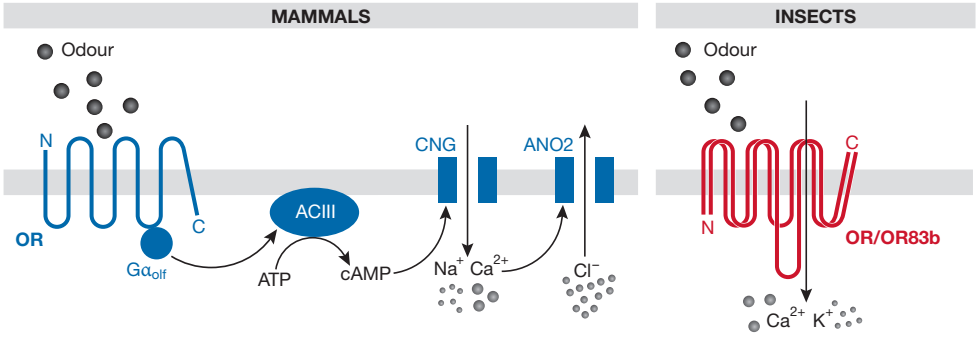

Fig 2 | Signalling mechanisms of mammalian and insect odorant receptors. A schematic of the molecular basis of olfactory signal transduction in the mouse and fruit fly. ACIII, type III adenylyl cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; ANO2, anoctamin 2 channel; CNG, cyclic nucleotide-gated channel;.$G\alpha_{olf}$, olfactory G protein α-subunit; OR, odorant receptor.

domain in IRs suggests that these receptors signal ionotropically, although this is yet to be confirmed.

Here, we consider the potential molecular, physiological, evolutionary and ecological reasons for why mammals and insects seem to use fundamentally different chemosensory receptors, although we acknowledge that formal proof of the signalling mechanism of several mammalian and insect receptor families is still unavailable (Sidebar A). A reflection on these possibilities also leads to verifiable hypotheses to illuminate further the emerging mechanistic distinctions.

All in the timing?

Ionotropic and metabotropic signalling pathways are fundamentally different in their temporal properties. The former are usually faster, operating on a millisecond (ms) to sub-ms timescale, as ligand binding directly gates the ion channel. By contrast, metabotropic receptors have a longer latency, from a few tens to several hundred ms, owing to the necessity to produce second messengers and activate secondary effectors. However, as a consequence of these downstream effects, metabotropic signalling can have a much longer duration, from a few seconds to several minutes. Do such temporal distinctions occur in insect and mammalian chemosensory systems? Are they important for how chemical stimuli are detected?

Most available data concerns ORs, although comparison among studies is complicated by the use of different animal models, experimental systems and the receptors analysed. Insect ORs can produce odour-evoked currents with very short latencies (<20 ms) when expressed in heterologous cells (Sato *et al*, 2008), which are similar to the latencies of OR-dependent, stimulus-evoked action potentials in OSNs *in vivo* (<30 ms; de Bruyne *et al*, 1999). By contrast, electrophysiological studies of isolated mammalian OSNs, or those in an intact olfactory epithelium, have revealed much higher latencies of odour-evoked currents—from about 90 ms to several hundred ms (Firestein *et al*, 1993; Grosmaitre *et al*, 2006; Kleene, 2008; Spors *et al*, 2006). Metabotropic signalling cascades can achieve faster reaction times, as observed in the *Drosophila* visual system—in which response latency can be as short as 20 ms—but this example depends on a sophisticated scaffolding mechanism for phototransduction signalling components and might be unique (Hardie & Raghu, 2001). The rapid reactions of insect OSNs to environmental odours are certainly also assisted by peripheral morphological specializations. The most evident of these is the 'everted' nature of the insect nose, the sensory cilia of which are separated from external odours often by less than a micrometre. By contrast, most mammalian OSNs are separated from the environment by long nasal cavities.

The reason behind the rapid responses of insects might be the dynamics of odour stimuli that these small animals experience. Volatile chemicals are released from their sources in the form of plumes, which are characterized by the alternation of odour strands of high concentration—which last from as little as 10–20 ms in a given position—with 'clean' air gaps (Kaissling *et al*, 1987). To locate an odour source, flying insects sample the air frequently to determine their position in either odour strands or odourless air, while also determining the direction of the wind carrying these strands (Budick & Dickinson, 2006; Carde & Willis, 2008). In essence, insect OSNs—at least in this context—act as flux detectors rather than concentration sensors (Baker, 2009). Analyses of insect OSN responses to artificial odour plumes have demonstrated their ability to rapidly track the presence or absence of odours through changes in action potential frequency (Barrozo & Kaissling, 2002; Schuckel *et al*, 2009). Such fast behavioural responses require both the onset and the termination of cellular responses to the stimuli to be fast. In these cases, an ionotropic mechanism might also be advantageous, because the dissociation of an odour molecule from the receptor could lead to rapid channel closure. By contrast, the termination of

Sidebar A | In need of answers

(i) Do insect ORs and GRs function exclusively as ligand-gated ion channels *in vivo*? Do they also couple to second messenger cascades?
(ii) How are insect chemosensory-receptor-evoked neuronal signals amplified and terminated at the molecular level?
(iii) How conserved are the molecular mechanisms of signal transduction between different vertebrate chemosensory GPCRs?
(iv) How does regulation of mammalian chemosensory signalling contribute to higher order perception of stimuli?
(v) Do insect IRs and GRs, and mammalian taste receptors, form heteromeric complexes *in vivo* and, if so, what is the precise role of different subunits within these complexes?
(vi) When did insect and mammalian chemosensory receptors evolve, and what were the genetic ancestors of these different repertoires?

Glossary

cAMP	cyclic adenosine monophosphate
cGMP	cyclic guanosine monophosphate
CNG	cyclic nucleotide-gated channel
GPCR	G-protein-coupled receptor
GR	gustatory receptor (invertebrates)
GUR	gustatory receptor family (*Caenorhabditis elegans*)
iGluR	ionotropic glutamate receptor
IR	ionotropic receptor
OR	odorant receptor
T1R	taste receptor type 1
T2R	taste receptor type 2
TRC	taste receptor cell
TRP	transient receptor potential
V1R	vomeronasal receptor type 1
V2R	vomeronasal receptor type 2

metabotropic responses requires the degradation of second messenger molecules, introducing a lag between the offset of the stimulus and of the response. An efficient enzymatic inactivation of odours inside sensilla probably provides a complementary mechanism that promotes fast signal termination (Ishida & Leal, 2005).

The situation is different in mammals, in which odours are actively drawn into the nasal cavity by sniffing. This modified respiratory phase could be a means to increase stimulus concentration (Wesson *et al*, 2009) or to improve detection at near-threshold concentrations (Oka *et al*, 2009). Sniffing completely changes stimulus dynamics, possibly obviating a need for temporally sensitive OSN responsiveness. Metabotropic signalling mechanisms could in fact allow the integration of signals over time, such that increases in stimulus duration result in comparable increases in the magnitude of the neuronal response to those evoked by higher stimuli concentrations presented over a proportionally shorter time period (Firestein *et al*, 1993; Takeuchi & Kurahashi, 2002). This integrative capacity might enhance the sensitivity of the vertebrate olfactory system.

Notably, although the latency of mammalian OSN responses is longer compared with that of insect OSNs, it does not necessarily constrain the timing of behavioural responses. A single sniff can result in highly accurate behavioural decision-making in rats in less than 200 ms (Uchida & Mainen, 2003), not much more than the fastest documented reaction time of a moth to a sex pheromone (150 ms; de Bruyne & Baker, 2008). Thus, the use of ionotropic or metabotropic mechanisms could simply be related to which aspects of olfactory information are first collected—such as the presence or absence of a stimulus, or its precise concentration—rather than how quickly an animal reacts to it.

Amplifying and adapting to odours

Although ionotropic chemosensory receptors provide an elegantly simple way to convert chemical detection into neuronal activation, the multicomponent nature of metabotropic signalling pathways could allow for a more sophisticated regulation of odour-evoked neuronal currents. Signal amplification is one broadly accepted advantage of metabotropic GPCR signalling, which is conferred by the ability of a single cell surface receptor to activate multiple G proteins, each of which can activate several downstream effectors to lead to the production of many second-messenger molecules. However, vertebrate olfactory GPCRs have a surprisingly low probability of activating even a single G protein owing to the brief odorant dwell-time (Bhandawat *et al*, 2005); higher affinity ligand–receptor combinations could, of course, have different properties. Although the amplification of olfactory signals might not happen at the receptor level, it clearly occurs further down the pathway, during the activation of CNG and chloride channels (Kleene, 1997). As in other contexts, signal amplification presumably increases the overall sensitivity of vertebrate chemosensory neurons.

The metabotropic olfactory receptor cascade—and probably that of other vertebrate chemosensory GPCR mechanisms—provides numerous points of regulation for the termination or adaptation of odour-evoked signals. These might act directly on the receptor, for example through phosphorylation by G-protein-coupled receptor kinases and binding of β-arrestins (Dawson *et al*, 1993), but essentially every known component of the cascade—$G\alpha_{olf}$, adenylyl cyclase III, cAMP, CNG and Ca^{2+}—has intrinsic or extrinsic mechanisms for downregulation or modulation (Kleene, 2008). Such a complex regulatory network undoubtedly shapes the dynamics of odour-evoked signals, ultimately having an impact on how these are represented and interpreted in the brain (Laurent, 2002; Spors *et al*, 2006).

Ionotropic insect ORs presumably cannot amplify odour-evoked signals directly, although one *in vitro* study indicates that the secondary activation of a metabotropic cAMP/cGMP-dependent pathway by ORs could feedback positively on the co-receptor OR83b to produce a more sustained and larger current response to a stimulus (Wicher *et al*, 2008). Insect sensory neurons do not seem to have a higher detection threshold than their vertebrate equivalents, however, and even single pheromone molecules are enough to elicit OSN activity in moths (Kaissling & Priesner, 1970). Such observations indicate that the coupling between insect receptors and spike generation can be extremely efficient. Signal amplification in insects could occur mainly at the first olfactory synapse, where relatively weak and variable spike trains in OSNs stimulated by low odour concentrations are transformed into amplified and temporally robust responses in second-order neurons with no appreciable delay (Bhandawat *et al*, 2007; Schlief & Wilson, 2007; Wilson *et al*, 2004).

Electrical signal modulation, such as termination and adaptation, has been reported in insect chemosensory systems (de Bruyne & Baker, 2008), but its molecular basis is not understood. However, the intracellular regulation of ion channels by a variety of second messengers—such as ions, cyclic nucleotides and lipids—is well-characterized in many other contexts (Damann *et al*, 2008). Thus it is possible that ionotropic insect chemosensory receptors are major targets for regulatory cascades. Clearly, much remains to be determined to fully appreciate and compare the modulatory capacities of metabotropic and ionotropic signalling pathways, and their biological significance for chemosensory perception.

'Combinatorial coding' in receptor complexes

Historically, there has been substantial interest in determining how many types of chemosensory receptor are expressed in a particular sensory neuron—or, for the mammalian gustatory system, a non-neuronal TRC—as this has allowed the inference of its potential breadth of tuning and discriminability of ligands. However, studies of metabotropic and ionotropic receptors in other contexts have revealed many cases in which co-expressed subunits function together, rather than independently, to create heteromeric

complexes with properties not exhibited by any individual subunit (Hille, 2001; Milligan, 2007). Do chemosensory GPCRs and ion channels use subunit combinations to define or expand their functional properties?

Most mammalian olfactory GPCRs are probably expressed uniquely in a given OSN, which indicates that heteromeric complex formation is unlikely (Mombaerts, 2004). Studies of ORs in heterologous systems indicate that some can form complexes with other non-olfactory GPCRs but the physiological relevance of these complexes *in vivo* has not been elucidated (Bush *et al*, 2007; Hague *et al*, 2004).

By contrast, mammalian gustatory GPCRs are one of the most striking examples of GPCR heteromerization, which has an impact on their functional properties (Chandrashekar *et al*, 2006; Yarmolinsky *et al*, 2009). Sweet-sensing TRCs express two T1R family members: T1R2 and T1R3, which interact physically *in vitro* and are both necessary—and together sufficient—to mediate responses to sweet tastants *in vivo* (Nelson *et al*, 2001). A distinct population of TRCs dedicated to umami taste also express T1R3 in combination with T1R1; T1R1 can also form a complex with T1R3 *in vitro* and both receptors are necessary—and together sufficient—to mediate umami responses *in vivo* (Nelson *et al*, 2002). Thus, the exchange of one GPCR subunit—that is, T1R1 for T1R2—can radically alter substrate selectivity. However, T1R3 is not simply a 'silent' partner, as the ligand-binding domains of both T1R2 and T1R3 can interact with sugars *in vitro* (Nie *et al*, 2005), and T1R3 can alone mediate responses to a high concentration of sugars *in vivo* (Zhao *et al*, 2003).

T2R bitter taste receptors exhibit the opposite extreme to olfactory receptors: the entire repertoire is potentially co-expressed in every TRC (Chandrashekar *et al*, 2006; Yarmolinsky *et al*, 2009). Different T2Rs recognize different bitter ligands and there is no evidence that they function in a combinatorial fashion. Thus, co-expression might confer a broad response profile on each individual bitter-sensing TRC.

The many examples of receptor co-expression for both olfactory and gustatory ionotropic insect receptors hint at the importance of combinations in sensory function. The best-studied case is that of OR83b, a highly conserved member of the repertoire that seems to be co-expressed with all other ORs (Benton *et al*, 2006; Larsson *et al*, 2004). OR83b forms a heteromeric complex with ligand-binding ORs and is essential to target them to the sensory cilia (Benton *et al*, 2006). OR83b might also form an integral part of the ion channel pore (Wicher *et al*, 2008). Assigning central cellular and signalling functions to a single member of the repertoire might allow ligand-specific ORs greater flexibility to evolve new odour specificities without compromising the signal transduction function of the OR–OR83b heteromer.

The dependence of insect sugar-sensing and bitter-sensing neurons on taste receptor combinations is probably more complex than that of their counterparts in mammals, as both types of sensory neuron express several (~5–10) different GRs, and loss-of-function genetic studies have demonstrated the requirement for up to three different receptors in mediating responses to specific tastants (Montell, 2009). Moreover, no *in vivo* reconstitution of taste receptors has been reported, suggesting that a functional receptor complex incorporates additional GRs.

An initial expression map of IRs revealed that some neurons might express 2–5 receptors, which is consistent with at least some IRs acting in heteromeric complexes (Benton *et al*, 2009). This would be analogous to the function of iGluRs in many variants of heterotetrameric complexes, the precise subunit composition of which is crucial in defining transport properties, ligand specificity, permeability and desensitization dynamics (Mayer & Armstrong, 2004). Could subunit-dependent properties also be relevant to insect chemosensory receptor complexes? Varied receptor-dependent temporal dynamics of insect OSN responses have been reported both in IR-expressing and OR-expressing neurons (de Bruyne *et al*, 2001; Hallem *et al*, 2004; Yao *et al*, 2005). Perhaps the heterogeneity in insect chemosensory receptor complexes compensates for the lack of downstream signalling components, to define neuron-specific dynamic properties of ligand-evoked responses.

In conclusion, although subunit combinations might be used by both GPCR and ionotropic chemosensory receptors, there seems to be greater potential for ion channel subunits to combine in functionally distinctive ways.

A just-so story?

Beyond mechanistic explanations, the dichotomy in signalling strategies could reflect a mere chance of evolution. Chemosensory repertoires can rapidly expand and diversify, as shown by the dramatic differences that exist between even closely related species (Nei *et al*, 2008). Therefore, the crucial event in determining the class of receptor that provides chemosensory abilities is probably the initial selection of a founding chemosensory receptor gene. Both GPCRs and ion channels are ancient protein families that were present before the divergence of animals. Thus, the genetic substrates to make this 'choice' of chemosensory signalling mechanism were certainly available to the ancestors of insects and mammals. As insects seem to be the exception of animal chemosensory transduction, we will consider the origins of their receptor repertoires.

The IRs could have evolved very early, as iGluR/IR-like genes are present across animal, plant and prokaryotic genomes (Chiu *et al*, 1999). In bacteria, it is probable that iGluRs have at least an analogous role to IRs in peripheral chemosensing of amino acids (Chen *et al*, 1999). Whether the ancestral function of animal iGluRs was in synaptic transmission and *Drosophila* evolved divergent members to fulfil roles in environmental chemical sensing, or if ancestral chemosensing iGluRs/IRs were progressively lost and/or specialized in mammals as GPCRs became predominant in providing their olfactory and gustatory needs, is unknown. Comparative genomics and expression analysis of iGluRs/IRs across metazoans could distinguish between these possibilities.

The dissimilarity of insect ORs and GRs to known classes of ion channel prevents definitive conclusions of their evolutionary history, but the existence of a few distant relatives in the nematode worm *Caenorhabditis elegans*—the GURs (Robertson *et al*, 2003)—indicates that they were present in the common ancestor of ecdysozoans. However, whether GURs also function in chemosensation is unclear (Edwards *et al*, 2008; Moresco & Koelle, 2004), and this organism has an enormous number of chemosensory GPCRs (Thomas & Robertson, 2008). *C. elegans* has an atypical chemosensory system organization, with dozens of receptor genes co-expressed in individual sensory neurons, which couple to common signal transduction cascades (Bargmann, 2006). Perhaps such organization, in which different receptor proteins are competing for space in the limited ciliary membranes, demands the amplification

mechanisms offered by metabotropic signalling to produce sensitive responses. Thus, although nematode ancestors potentially had the choice of GPCRs and insect-like chemosensory receptors, the former class ultimately fulfilled the requirements for chemical sensing by their particular nervous systems.

Finally, we note that the independent appearance of two fundamentally different chemosensory ion channel families in insects—GR/ORs and IRs—at potentially different times in evolution, argues against the emergence of the observed dichotomy by 'chance', and rather points towards the specific mechanistic advantages of the ionotropic signalling mechanism for insect chemosensation.

Closing remarks

Although we have highlighted the distinctions between insects and mammals, there is evidence for some conserved chemosensory receptors, such as members of the ionotropic TRP channel repertoire, which have been variously implicated in the perception of sour, pungent or spicy chemical stimuli in mice and *Drosophila* (Damann *et al*, 2008), and guanylyl cyclases, which mediate detection of various environmental gases in these animal classes through the cGMP second messenger (Luo *et al*, 2009). The existence of such parallels is consistent with the significant molecular conservation observed in other sensory modalities—such as opsins in the visual system (Fernald, 2006)—and central neuronal communication mechanisms (Ryan & Grant, 2009), and reinforces the need to consider why the fly on your banana smells and tastes it—at least mechanistically—quite differently from you.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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