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Smell and taste on a high

Symposium on Chemical Senses: From Genes to Perception

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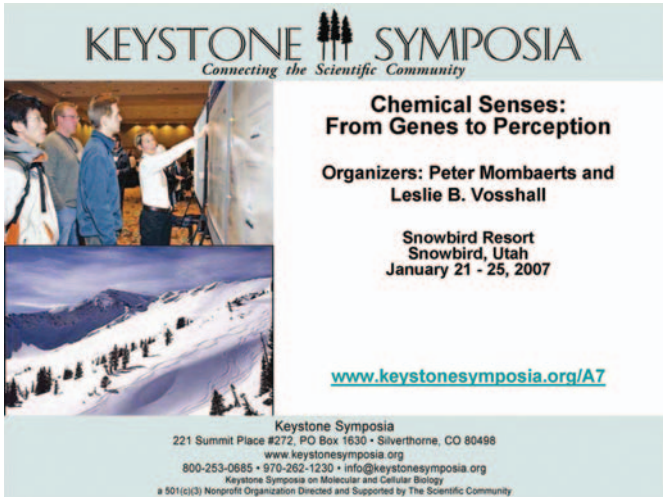

The first Keystone Symposium on Chemical Senses: From Genes to Perception took place between 21 and 25 January 2007, in Snowbird, Utah, USA, and was organized by P. Mombaerts and L.B. Vosshall.

Keywords: olfaction; gustation; receptor; pheromone; behaviour

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Introduction

Since the origin of life in the primordial soup, the survival of all organisms has depended on their ability to detect and respond to chemicals in their environment. Today, animal chemosensation—smell and taste—relies on sensory circuits that recognize diverse external chemical cues and transform them into precise patterns of neuronal activity to evoke the appropriate response (Ache & Young, 2005; Hildebrand & Shepherd, 1997). In contrast to the visual or auditory systems, determining how chemosensory stimuli are processed in the brain has relied heavily on molecular approaches (Julius & Katz, 2004). The identification of chemosensory receptor genes in vertebrates and invertebrates, pioneered by the Nobel Prize-winning discovery of the mammalian odorant receptors (ORs) in 1991 (Buck & Axel, 1991), has provided the foundation for a genetic dissection of the organization and function of these sensory circuits. This Keystone Symposium brought 148 scientists to Snowbird, Utah, USA, to discuss the latest advances in the field. The four-day meeting, framed by keynote lectures from L. Buck (Seattle, WA, USA) and R. Axel (New York, NY, USA), integrated a broad spectrum of topics, including receptor genomics and genetics, the developmental biology and physiology of chemosensory circuits, and chemosensory-driven behaviours.

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Receptors, receptors everywhere

The chemosensory receptors of an animal determine which molecules it can smell and taste; however, receptor repertoires must constantly adapt to the changing chemical stimuli that organisms face throughout evolution. For example, animals might encounter new food sources or predators, and might develop—or lose—social interactions based on chemical communication (Bargmann, 2006). S. Firestein (New York, NY, USA) and B. Trask (Seattle, WA, USA) presented cross-mammal comparisons of both the ORs and the V1R and V2R families of putative pheromone receptors (Young *et al,* 2005; Young & Trask, 2007; Zhang *et al,* 2007). The V1Rs contain much more variation than ORs and form many more species-specific subfamilies, which is consistent with a role for the former in mediating intraspecific social interactions. The V2R repertoires are also divergent and exhibit remarkable degeneration in primates, cows and dogs. The challenge now is to define the functional significance of these patterns of conservation and divergence. Few ligands are known for these receptors, although a solution to this problem is available, at least for the ORs. H. Matsunami (Durham, NC, USA) described the development of an *in vitro* receptor expression system using recently identified OR chaperones (Saito *et al,* 2004; Zhuang & Matsunami, 2007). This promises to allow de-orphanization of large numbers of ORs and provide an insight into their roles *in vivo*.

ORs, V1Rs and V2Rs are apparently not the whole story. Buck described a new candidate olfactory receptor family, the trace

amine-associated receptors (TAARs; Liberles & Buck, 2006). TAARs respond *in vitro* to volatile amines present in mouse urine, which might function as social cues indicating sexual maturity or stress. These findings, together with the recent mapping of sensory inputs into reproductive circuits (Boehm *et al,* 2005; Yoon *et al,* 2005), blur the traditionally accepted functional distinction between the roles of the vomeronasal organ—which expresses V1Rs and V2Rs—as the pheromone sensor and the main olfactory system—which expresses ORs and TAARs—as the sensor of environmental odours.

Beyond traditional model systems, genomic sequences are opening up olfactory research in many other organisms. B. Kempenaers (Seewiesen, Germany) identified a broad range of avian ORs. Their existence suggests that in addition to their visual and auditory abilities, which allow communication through brilliant plumage or sophisticated mating calls, birds are also likely to have a good sense of smell. L. Zwiebel (Nashville, TN, USA) described the OR repertoire in the mosquito *Aedes aegypti*, the primary arthropod vector for yellow fever and dengue viruses. He noted that few of its ORs have obvious orthologues in the malaria mosquito *Anopheles gambiae*, perhaps reflecting the adaptation of the olfactory abilities of these species to different ecological niches.

Significant changes in an OR repertoire are, however, not a prerequisite for major changes in the lifestyle of an animal. B. Hansson (Jena, Germany) documented the odour-response profiles of a large fraction of olfactory sensory hairs in nine members of the *melanogaster* subgroup of *Drosophila*. Despite the distinct niches inhabited by different species, their olfactory responses are similar (Stensmyr *et al,* 2003), presumably reflecting conservation in the sequence and expression patterns of the underlying ORs. One exception was observed in *D. sechellia*, which is endemic to the Seychelles and lays its eggs exclusively on morinda fruit. Hansson showed that such behavioural changes might be at least partly accounted for by increases in both the number and sensitivity of sensory neurons expressing Or22a, a receptor for a major volatile of this fruit (Dekker *et al,* 2006).

Chemical recognition beyond G-protein-coupled receptors

Almost all known olfactory and gustatory receptors, except probably those in insects (Benton *et al,* 2006; Wistrand *et al,* 2006), belong to the G-protein-coupled receptor (GPCR) superfamily. However, such dominance might reflect an experimental bias as most efforts to identify chemosensory receptors have used strategies aimed at isolating new GPCRs. C. Zuker (San Diego, CA, USA) described an unbiased bioinformatics screen for new mammalian taste receptors, which identified polycystic kidney disease 2-like 1 (PKD2L1), a member of the transient receptor potential (TRP) family of ion channels (Huang *et al,* 2006). Zuker showed that PKD2L1, together with a second TRP channel PKD1L3, is expressed in a population of taste-receptor cells distinct from those mediating sweet, umami and bitter tastes. Genetic ablation of these cells specifically abolishes physiological responses to sour tastants. These data, together with functional characterization of these receptors *in vitro* (Ishimaru *et al,* 2006), strongly implicate PKD2L1/PKD1L3 as a sour-taste receptor.

L. Macpherson (San Diego, CA, USA) introduced another TRP channel, TRPA1, which was initially identified through its role in thermosensation. TRPA1 is also activated by several noxious chemicals, such as mustard oil and allicin (the pungent component of garlic), which implicates this channel in chemesthesis, the somatosensory contribution to taste. Macpherson showed that such chemicals covalently modify cysteine residues within the amino terminus of the channel. This reaction evokes rapid and sustained channel activation, revealing a new mechanism of chemical detection (Macpherson *et al,* 2007).

Although transmembrane receptors have been the natural focus of investigations into chemosensory detection, increasing evidence suggests that perireceptor proteins also have important functions. Y. Oka (Tokyo, Japan) described an *in vivo* OR identification strategy for receptors for eugenol and related odours (Oka *et al,* 2006). Notably, when tested *in vitro*, the identified ORs exhibited altered ligand specificity and much lower sensitivity. Oka showed that the presence of olfactory mucus could partly explain this discord. Mucus is rich in odorant-binding proteins (OBPs) and cytochrome P450 enzymes, raising the possibility that such perireceptor proteins have a role in modulating olfactory sensitivity and specificity. Indeed, recent studies on *Drosophila* provided the first genetic evidence for an essential role for an OBP, named LUSH, in the detection of the pheromone *cis*-vaccenyl acetate (cVA; Xu *et al,* 2005). J. Laughlin (Denver, CO, USA) presented the crystal structure of a LUSH–cVA complex, providing insight at the atomic level into how LUSH binds pheromone molecules. Clearly, there is still much to learn about the passage of chemical stimuli from the environment to the sensory receptors.

Wiring smell in the brain

Chemosensory systems pose problems of general significance to neurobiology, such as the neuronal guidance mechanisms that must exist to direct the precise convergence of axons of olfactory sensory neurons (OSNs) expressing the same OR into discrete glomeruli in the olfactory bulb (Mombaerts, 2006). In mammals, ORs themselves have long been known to have an instructive function in axon guidance (Mombaerts *et al,* 1996). Recent analysis revealed that OR proteins are indeed present in OSN axons and that both the level of OR expression and single amino-acid polymorphisms in OR sequences influence axon sorting (Feinstein *et al,* 2004). These data suggested a model in which ORs direct the convergence of like OSNs by mediating homotypic axon–axon interactions (Feinstein & Mombaerts, 2004). However, at this meeting, A. Chesler (New York, NY, USA) and H. Sakano (Tokyo, Japan) presented results that suggest a different model in which OR-dependent signalling in OSNs, rather than the OR protein itself, regulates axonal targeting (Chesler *et al,* 2007; Imai *et al,* 2006). Sakano showed that a mutant OR lacking a G_{α}-binding site is unable to promote axonal convergence into a glomerulus. This defect can be rescued, however, by expression of a constitutively active $G_{\alpha S}$ subunit in these neurons. Chesler showed that ectopic expression of constitutively activated $G_{\alpha S}$, by retroviral injection into the embryonic olfactory epithelium, in random OSNs is sufficient to promote convergence of their axons, although they presumably express different ORs. $G_{\alpha S}$ stimulates adenylyl cyclase type 3 (AC3) to produce cAMP. Analysis of an AC3 mutant by Chesler (Fig 1) and a constitutively active cAMP-dependent protein kinase A by Sakano provided further support for a role for the cAMP signalling pathway in axonal convergence. Importantly, Sakano showed that modulation of cAMP levels in OSNs affects where they will form glomeruli along the anterior–posterior axis of the olfactory bulb. This suggests that cAMP signals in OSNs define the global patterning of axon projections. The segregation of axons into hundreds of distinct glomeruli is likely to require additional local sorting mechanisms. An independent study

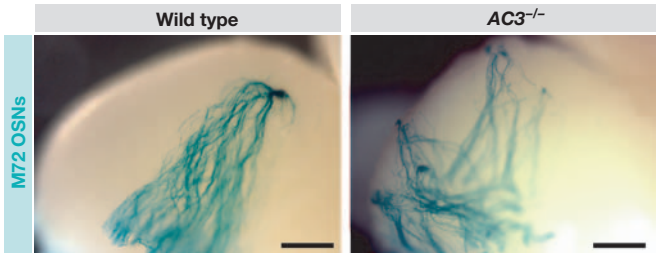

Fig 1 | cAMP signalling is essential for glomerular convergence of olfactory sensory neurons in the olfactory bulb. Axonal projections of OSNs expressing the odorant receptor M72 (labelled with tau-lacZ and visualized by X-gal staining) in wild-type and *AC3* null mutant ($AC3^{-/-}$) mice. In wild-type animals, M72 axons converge into a single glomerulus. By contrast, in *AC3* mutants, M72 projections are highly disrupted with axons found in numerous atypical locations in the olfactory bulb. Scale bars, 0.5 mm. Images courtesy of D.-J. Zou and A. Chesler (© 2007 The National Academy of Sciences of the USA; Chesler *et al*, 2007). *AC3*, adenylyl cyclase type 3; OSNs, olfactory sensory neurons.

presented by Sakano identified a potential role for the homophilic transmembrane adhesive proteins Kirrel2 and Kirrel3, and the repulsive proteins ephrin A5 and EphA5 in this process (Serizawa *et al,* 2006). The expression level of these genes in OSNs correlates with which OR is expressed and is regulated by neuronal activity. These molecules might therefore provide a link between OR-specific signalling and the physical segregation of like axons into unique glomeruli.

Pheromones for fun and fear

Since the isolation of the first pheromone 50 years ago—the silk moth sex attractant bombykol—chemical communication between members of the same species has been an intense field of investigation. The recent identification of pheromone receptors in *Drosophila* has allowed genetic analysis of how intraspecific signals are encoded in the brain.

B. Dickson (Vienna, Austria) described the role of the receptor Or67d and its ligand cVA, a male-specific volatile pheromone, in male courtship behaviour (Kurtovic *et al,* 2007). *Or67d* mutant males court females normally, and also readily court other males. This suggests that cVA signalling through Or67d neurons inhibits male–male courtship. Furthermore, application of cVA on the abdomen of virgin female flies, which simulates the pheromone transfer that occurs during mating, suppressed their courtship by wild-type males. This inhibitory effect could also be achieved by artificial activation of Or67d neurons through ectopic expression of the bombykol receptor, BmOR1 (Nakagawa *et al,* 2005), in these cells and through the painting of females with bombykol. These results reveal that Or67d neurons are both necessary and sufficient in males to inhibit the courtship of other males and non-virgin females.

H. Amrein (Durham, NC, USA) presented an analysis of a second receptor, Gr32a, which seems to have a similar role to Or67d in inhibiting male–male courtship. This receptor is expressed in contact chemosensory neurons on the labial palps and the forelegs, and might therefore recognize a non-volatile male cuticular hydrocarbon pheromone. Notably, Gr32a is related to Gr68a, a receptor Amrein has previously shown to be required for male courtship of females (Bray & Amrein, 2003). Therefore, both stimulatory and inhibitory pheromonal signals are used to direct males to the appropriate mate.

Pheromones also signal danger. For example, the *Drosophila* stress odour (dSO), introduced by D. Anderson (Pasadena, CA, USA), is released by mechanically agitated flies and triggers avoidance behaviour in other flies. One component of dSO is CO_2, which evokes this behaviour through the stimulation of Gr21a OSNs (Suh *et al,* 2004). Anderson showed that these neurons are also sufficient to provoke the avoidance response by artificially activating them with the light-sensitive channel rhodopsin.

These analyses reveal that a single type of OSN can induce pheromone-evoked behaviours. This is in contrast to the combinatorial code of sensory input that is believed to underlie general odour discrimination. However, pheromone coding is similar to the 'labelled-line' mechanism that underlies taste perception, in which taste-receptor cells respond to specific taste qualities and are wired to elicit stereotypic behavioural responses (Chandrashekar *et al,* 2006; Wang *et al,* 2004). It is intriguing to speculate that taste and pheromone sensory systems have a common evolutionary origin. This is likely to be true in insects, as Amrein's inhibitory pheromone receptor, Gr32a, is expressed in a subset of bitter-taste-sensing neurons. Therefore, courtship with the wrong sex might provoke the same perception in the brain as a bitter taste.

Many mammalian behaviours are also dictated by pheromones, but it has proven to be a challenge to link specific ligands to receptors and sensory pathways. K. Touhara (Tokyo, Japan) highlighted one of these aspects through his identification of a peptide family in rodents, the exocrine gland-secreting peptides (ESPs). Cellular and electrophysiological analysis of ESP-induced responses in the vomeronasal organ revealed that this family is likely to represent the long sought-after ligands for the V2R pheromone receptors (Kimoto *et al,* 2005). Although the behaviours controlled by ESPs remain to be determined, Touhara showed that several members are expressed in a sex-specific and sex-hormone-regulated manner, suggesting that they have a role in sexual communication.

K. Kobayakawa (Tokyo, Japan) dramatically illustrated the behavioural effects elicited by a pheromone—or, more correctly, a kairomone—in a video of a petrified mouse up against the wall at the far end of its enclosure from a source of 2,4,5-trimethylthiazoline (TMT), a characteristic fox odour. Similar to dSO responses in *Drosophila*, this freezing behaviour seems to be evoked by input into specific olfactory channels: animals lacking a defined zone of OSNs do not exhibit this response, although additional tests indicate that they could still detect TMT through other olfactory pathways.

Chemotaxis coding

Although pheromone-evoked innate behaviours are striking to witness, the ability of an organism to perform an 'ordinary' behaviour such as chemotaxis toward food odours requires perhaps even more sophisticated chemosensory processing abilities. J. Porter (Berkeley, CA, USA) and L. Vosshall (New York, NY, USA) dissected chemotaxis in two very different organisms: humans and *Drosophila* larvae (Fig 2). Porter challenged blindfolded human subjects to follow a chocolate essential-oil trail by sniffing. Contrary to popular ideas about our poor olfactory abilities, the task was performed impressively well. Porter went on to show that left and right nostrils sample spatially distinct air space, and that the performance of a subject was compromised when airflow was converged, by using a nasal adapter, before entering their nostrils. These results suggest

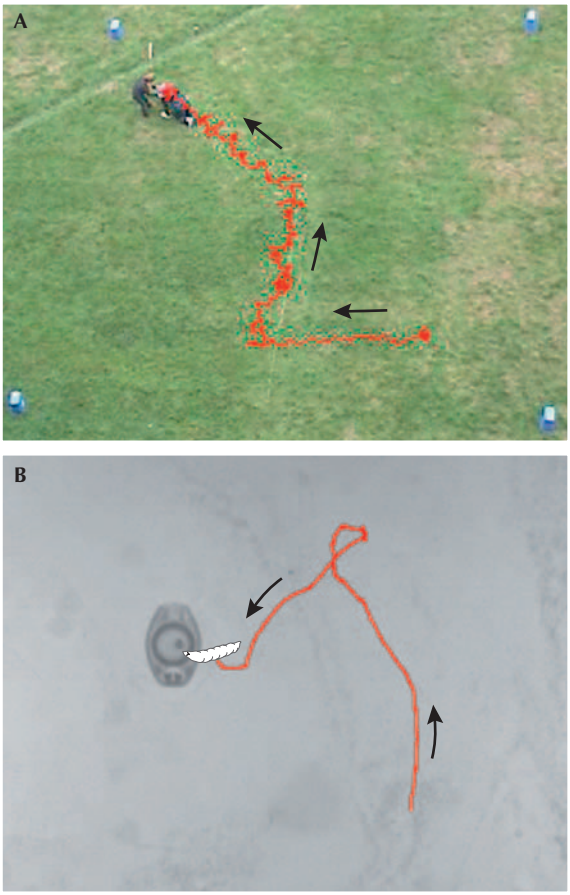

Fig 2 | Scent-tracking in humans and maggots. (**A**) Tracking of a trail of chocolate essential oil (faint white line) by a human subject in an open 10 m × 10 m arena (corners marked by blue squares). The track (red line) represents 5 min 34 s. Image courtesy of J. Porter. (**B**) Chemotaxis of a *Drosophila* larva across an agarose surface towards 50 µl isoamyl acetate (banana odour) in the cap of a centrifuge tube. The track (red line) represents 20.7 cm covered over 3 min 50 s. Image courtesy of M. Louis.

that inter-nostril comparisons assist scent-tracking, which is perhaps analogous to the role of binocular vision in conferring depth perception (Porter *et al,* 2007).

Vosshall described manipulations of sensory input into the minute nose of the *Drosophila* larva using genetic rather than physical tools (Fishilevich *et al,* 2005). The nose comprises 21 bilaterally symmetrical pairs of OSNs, but Vosshall showed that animals with only a single pair can chemotax up an odour gradient. Therefore, although many types of OSN might respond to a given odour, information about changing stimulus concentrations can be encoded in single neurons.

The relative simplicity of the nervous system of *Caenorhabditis elegans* has allowed enviable progress to be made in delineating complete circuits, from sensory input to motor output, which mediate taxis behaviours. C. Bargmann (New York, NY, USA) described quantitative tracking assays that revealed that worms chemotax by using a biased random walk, analogous to bacterial chemotaxis, in which the frequency with which they turn, or 'pirouette', is inversely correlated with odour concentration (Gray *et al,* 2005; Pierce-Shimomura *et al,* 1999). By using laser ablations and genetic manipulation of the signalling properties of specific cells, Bargmann showed that sub-routines of this behaviour could be assigned to individual neurons in the circuit. Physiological correlates of these properties are now being examined by calcium imaging. Notably, sensory neurons exhibit transient responses, whereas the activity of certain inter-neurons persists longer, suggesting a transition from brief sensory input to longer-lasting behaviours.

Concluding remarks

This meeting highlighted the remarkable progress in our understanding of the peripheral mechanisms of chemosensation. However, as Axel eloquently articulated in his closing lecture, the future challenge will be to address how chemosensory information is processed and interpreted centrally in the brain. Knowledge of chemosensory receptor genes opened up the analysis and control of peripheral sensory neurons, but such specific molecular markers are not yet known—or might not even exist—for higher-order circuit elements. Nevertheless, tools to map central circuits are being developed, such as trans-synaptic tracers described by Buck (Boehm *et al,* 2005; Zou *et al,* 2001) and a photoactivatable green fluorescent protein introduced by Axel. Together with ever-improving genetically encoded reporters and stimulators of neuronal activity, these techniques promise to allow the visualization and manipulation of chemosensory circuits deep within the brain. It will be exciting to attend the next Symposium of this series in 2009 (touch wood) to see and hear how we smell and taste.

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