doi: http://dx.doi.org/10.5016/1806-8774.2009v11pT86

ARBS Annual Review of Biomedical Sciences

Theme Topic on "Cell Receptors and Signaling"

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2009;11:T86-T94

The Odorant Signaling Pathway

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Received: 03 June 2009; accepted 22 December 2009
Online on 21 February 2010

Abstract

Malnic B, Mercadante AF. The Odorant Signaling Pathway. Annu Rev Biomed Sci 2009;11:T86-T94. Through the sense of smell mammals can obtain information about food, danger, sexual partners and predators. Two main different types of signals can be recognized by the olfactory system: volatile odorants, which are detected by the olfactory sensory neurons of the nose; and pheromones, which are detected by the vomeronasal neurons of the accessory olfactory system, or vomeronasal organ. These sensory neurons express respectively hundreds of odorant and pheromone receptors, which belong to the superfamily of G protein-coupled receptors. We review the general organization of the main and accessory olfactory systems, the structures of the receptor families in each of these organs and their signaling pathways.

Keywords: olfaction, odorant receptors, GPCRs, pheromone receptors, vomeronasal organ, Ric-8B, Gγ13.

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1. Introduction: the Olfactory System

Using the sense of smell mammals can detect and discriminate between large numbers of volatile environmental chemicals. These chemosignals provide important information that is critical for survival, reproduction and social interactions. Odorants are typically small organic molecules of less than 400 Da, with various sizes, shapes, functional groups and charges. They are first detected in the upper

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region of the nose, by the main olfactory epithelium (MOE) (Fig. 1). In this region, millions of olfactory sensory neurons (OSN) interact with odor molecules (Buck, 1996) through the odorant receptors (OR). The ORs are proteins that belong to the superfamily of G protein-coupled receptors (GPCRs) (Buck & Axel, 1991), which are localized in the cilia, specialized hairlike structures of the OSN dendrite. The binding of odors to the ORs initiates an electrical signal that travels along the axons to the main olfactory bulb (MOB) (Fig. 1). The information is then passed on to other regions of the brain, leading to odorant perception and emotional and behavioral responses (Buck, 1996).

In addition to the main olfactory system, most mammals have an accessory olfactory system, which is responsible for pheromone detection and signaling (Dulac & Torello, 2003). Sensory neurons in the accessory system are found within the vomeronasal organ (VNO), a blind-ended tube, which lies above the hard palate and at the base of the nasal septum (Fig. 1) (Doving & Trotier, 1998). The vomeronasal sensory neurons (VSNs) send their axons to synapse with second order neurons, in the accessory olfactory bulb (AOB) (Fig. 1) (Brennan & Keverne, 2004). Two distinct families of GPCRs, unrelated to ORs, were found to be expressed in the VNO and are named V1Rs and V2Rs, for class 1 and class 2 vomeronasal receptors, respectively. The apical VNO neuroepithelium contains V1R-expressing neurons and the basal VNO contains V2R-expressing VSNs (Fig.. 1) (Dulac & Torello, 2003). Anatomical and genetic evidences indicate that a functional accessory olfactory system is not maintained in higher primates, including humans (Brennan & Zufall, 2006).

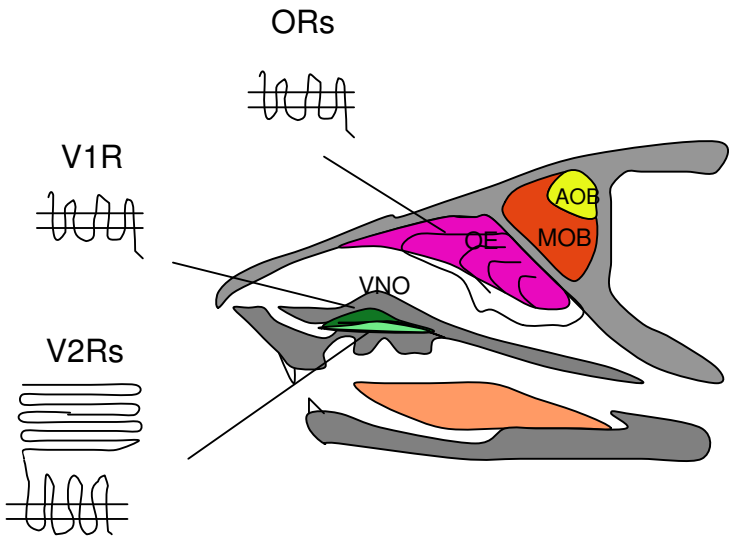

Figure 1. Schematic representation of the mouse olfactory system. Odorant receptors (ORs) are expressed by olfactory sensory neurons localized in the main olfactory epithelium (MOE). Vomeronasal type 1 receptors (V1Rs) are neurons localized in the apical region of the vomeronasal epithelium in the vomeronasal organ (VNO), while vomeronasal type 2 receptors (V2Rs) are expresses by neurons localized in the basal region of the vomeronasal epithelium. Olfactory sensory neurons project their axons to the main olfactory bulb (MOB) and vomeronasal neurons project their axons to the accessory olfactory bulb (AOB).

Several data suggested that the VNO acts as a conveyer of pheromone responses. Mice with VNO ablation show some behavior and physiological deficits in their response to chemosensory cues (Brennan & Keverne, 2004). Recent studies using genetically modified animals have elucidated the role of the accessory olfactory system in animal communication and behavior. For instance, targeted deletion of a large cluster of V1Rs produced mice with deficits in maternal and sexual behavior (Del Punta *et al.*, 2002). Moreover, mice deficient for the expression of the TRP2 (transient receptor potential

channel 2) cation channel, which is essential for signal transduction in VSNs, showed altered sexual and social behaviors (Leypold *et al.*, 2002; Stowers *et al.*, 2002).

It has been long believed that the MOE is specialized for detecting volatile, airborne structures, while the VNO would detect non-volatile chemosignals, such as those found in urine, skin, scent glands and reproductive secretions. However, a large number of observations indicate that this functional division is not absolute (revised in Brennan & Zufall, 2006). Some results using functional magnetic resonance imaging suggest that the mouse AOB responds to volatile urine odors (Xu *et al.*, 2005). Other studies demonstrated that the MOE also responds to non-volatile stimuli and to pheromones. The nipple-search pheromone, for example, is still effective in suckling rabbit pups even after VNO lesions (Hudson & Distel, 1986). Mice lacking the functional cyclic nucleotide-gated channel alpha 2 (CNGA2), which is required for odor-evoked MOE signaling, demonstrated behavioral deficits related to mating and aggressive responses. These data suggest an essential role for the MOE in regulating behaviors traditionally related to the VNO (Mandiyan *et al.*, 2005). More recent evidence has demonstrated that non volatile MHC peptide ligands are able to gain access to the MOE during behavioral situations involving direct physical contact (Spehr *et al.*, 2006). Using mice with targeted deletions in the CNG channel subunits, Spehr *et al.* (2006) have verified that the MOE cAMP-dependent signal transduction is crucial for the detection of MHC peptides ligands and that this signal is related to social recognition *in vivo*. Therefore, MOE and VNO have complementary roles in chemosignal detection and signaling.

2. Odorant and Pheromone Receptors are GPCRs

The ORs belong to the super-family of G-protein coupled receptors, and have seven putative transmembrane domains, a short extracellular N-terminal domain and a short intracellular C-terminal domain. Members of the OR family are extremely diverse in their amino acid sequences. The nucleotide sequence identity among the coding regions ranges from 34-99% (Godfrey *et al.*, 2004; Malnic *et al.*, 2004), consistent with the ability to recognize a large variety of odorants.

The odorant receptor genes constitute the largest gene families in mammalian genomes, with around 1,000 functional receptors in rodents (Young *et al.*, 2002; Godfrey *et al.*, 2004; Zhang *et al.*, 2004; Niimura & Nei, 2005) and 400 functional receptors in humans (Glusman *et al.*, 2001; Niimura & Nei, 2003; Malnic *et al.*, 2004). There are also large numbers of OR genes that are pseudogenes, which do not express functional ORs. The number of pseudogenes varies among species: while humans have around 460-480 pseudogenes (Glusman *et al.*, 2001; Zozulya *et al.*, 2001; Niimura & Nei, 2003; Malnic *et al.*, 2004), mice have around 250-330 pseudogenes (Young *et al.*, 2002; Godfrey *et al.*, 2004; Zhang *et al.*, 2004; Niimura & Nei, 2005).

I*n situ* hybridization experiments have initially indicated that each olfactory sensory neuron expresses only one out of the 1,000 odorant receptor genes (Ressler *et al.*, 1993; Vassar *et al.*, 1993). This was later verified by examining gene expression in single neurons by single cell reverse transcription-polymerase chain reaction (RT-PCR) (Malnic *et al.*, 1999). Neurons expressing one same given OR converge onto two or few glomeruli at two specific sites in the olfactory bulb (Ressler *et al.*, 1994; Vassar *et al.*, 1994). Interestingly, specific glomeruli show approximately the same locations in different individuals. These results indicate that the information provided by different ORs in the nose is organized into a stereotyped sensory map in the olfactory bulb.

Both V1R and V2R families also have the characteristic GPCR serpentine architecture. Differently from the ORs or V1Rs, the V2Rs have a large extracellular N-terminal domain (Fig. 1), The VRs are expressed by vomeronasal neurons that are located in two different layers of cells in the vomeronasal epithelium. Neurons located in the apical region of the epithelium coexpress the G protein subunit Gαi2 together with members of the V1R family. Neurons located in the basal layer of the epithelium coexpress the G protein subunit Gαo together with members of the V2R family (Fig. 1). The mouse V1R family consists of about 187 intact genes (Rodriguez *et al.*, 2002; Zhang *et al.*, 2004; Young *et al.*, 2005; Shi & Zhang, 2007). In humans, the vast majority of the V1R genes are pseudogenes, while only five are intact V1R genes (Rodriguez *et al.*, 2000; Rodriguez & Mombaerts, 2002). In mice, the V2R family is constituted of 121 intact genes (Shi & Zhang, 2007; Young & Trask, 2007). In humans, however, no intact V2R gene has been identified.

Interestingly, the one neuron-one receptor rule observed for ORs also applies for the vomeronasal receptors: each vomeronasal neuron expresses only one single member of the V1R or V2R families. The precise mechanisms involved in the regulation of OR or VR gene expression remain, however, unknown. The ligands for the V1Rs and V2Rs are not well known. Experiments so far indicate that while V1Rs respond to volatile pheromones (Leinders-Zufall *et al.*, 2000; Del Punta *et al.*, 2002) or odorants (Sam *et al.*, 2001), the V2Rs respond to nonvolatile pheromones such as peptides or proteins (Touhara, 2007).

Recently two small additional families of GPCRs expressed in olfactory or vomeronasal sensory neurons were identified. The trace amine-associated receptors (TAARs) are expressed in olfactory sensory neurons that do not express ORs (Liberles & Buck, 2006). Only one member of the TAAR family is expressed per neuron, in a similar monogenic expression pattern shown by ORs and VRs. These receptors respond to biogenic amines, some of which are found in the male mouse urine, a known source of pheromonal cues (Liberles & Buck, 2006). These results suggest that TAARs may work as pheromone receptors. However, it remains to be demonstrated whether TAARs are really required for specific mouse behaviors. Interestingly the TAAR genes are found in many vertebrate genomes, including humans (Liberles & Buck, 2006).

Formyl peptide receptor (FPR) gene family are GPCRs normally found in immune cells, where they mediate responses to cell damage and inflammation (Migeotte *et al.*, 2006). Five members of this GPCR family were shown to be expressed in vomeronasal neurons that do not express V1Rs or V2Rs (Riviere *et al.*, 2009). These receptors also show a monogenic and punctate pattern of expression in the sensory neuroepithelium, reminiscent of that displayed by ORs and V1Rs. The identification of FPR expression in vomeronasal neurons raises the interesting possibility that the VNO may also be involved in the detection of pathogens, spoiled food or sick animals. This possibility, however, remains to be proved.

Altogether, the results above show that different GPCR families are involved in olfaction. Possibly additional GPCRs expressed in the different olfactory organs, including the septal organ of Masera and the Grueneberg ganglion, which are located in distinct regions of the nose (Munger *et al.*, 2009), are yet to be discovered.

3. The Odorant Receptor Signaling Pathway

The transduction of chemical signals by ORs represents the initial step in a cascade of events that ultimately leads to the discrimination and perception of odorants. In the OSNs, different ORs transduce signals through a common pathway. Odorant binding to ORs leads to the activation of the associated specific heterotrimeric G-protein, Golf. The alpha subunit of olfactory G-protein Golf (Gαolf) exchanges GDP for GTP. The GTP-bound Gαolf dissociates from the Gβ/γ complex and activates adenylyl cyclase III to produce cAMP. Increased cAMP levels activate cyclic nucleotide-gated (CNG) channels, and the resulting influx of Na^+ and Ca^{2+} ions leads to the generation of an action potential in the olfactory neuron axon (Firestein, 2001; Ronnett & Moon, 2002; Mombaerts, 2004) (Fig. 2). The downstream components of the OR signaling, Gáolf, adenylyl cyclase III and cyclic nucleotide-gated channel are highly enriched in the cilia of OSNs (Ronnett & Moon, 2002) and the knockout mice for these three proteins are anosmic (Brunet *et al.*, 1996; Belluscio *et al.*, 1998; Wong *et al.*, 2000; Zheng *et al.*, 2000).

The olfactory system has evolved to detect rapid chemical signal changes in the environment. The odorant-induced production of cAMP is typically rapid and transient (Boekhoff *et al.*, 1990; Breer *et al.*, 1990). Desensitization mechanisms are important for different sensory systems and allow the olfactory system to detect over a broader range of stimuli and also to rapidly recover the ability to sense an odorant. Several molecular mechanisms for odor signal termination have been described, such as inhibition of adenylyl cyclase III (Wei *et al.*, 1998; Sinnarajah *et al.*, 2001), stimulation of cAMP hydrolysis by activation of phosphodiesterase (Borisy *et al.*, 1992; Yan *et al.*, 1995), CNG channel regulation (Chen & Yau, 1994; Kurahashi & Menini, 1997; Munger *et al.*, 2001) and odorant receptor phosphorilation and internalization (Boekhoff & Breer, 1992; Peppel *et al.*, 1997; Mashukova *et al.*, 2006).

We have described a possible regulation of the odorant signaling pathway through the olfactory G-protein Golf. A putative Guanine nucleotide Exchange Factor (GEF) named Ric-8B, that is specifically expressed in OSNs, interacts with Gαolf (Von Dannecker *et al.*, 2005) and amplifies OR signaling (Von Dannecker *et al.*, 2006). It was demonstrated that Ric-8B also interacts with Gγ13 (Kerr *et al.*, 2008), a divergent member of the Gγ subunit family which has been implicated in taste signal transduction (Huang *et al.*, 1999; Blake *et al.*, 2001). It was also shown that Gβ1 is the predominant Gβ subunit expressed in the OSNs (Kerr *et al.*, 2008). Ric-8B, Gαolf, Gγ13 and Gβ1 are co-localized in the cilia of OSNs and *in vitro* binding assays indicated that these four components are able to form a protein complex (Kerr *et al.*, 2008). Altogether, these results suggest two possible roles for Ric-8B in the odorant signal transduction *in vivo*. First, Ric-8B could act as an assembly factor that assists in the formation of Golf protein complex in the cilia of olfactory sensory neurons. Another possible physiological function for Ric-8B is that it would act as a GEF on the Gαolf and enhance the odorant signal transduction (Fig. 2). However, the exact role of Ric-8B should be determined and mice deficient for Ric-8B will be an important tool to address this question.

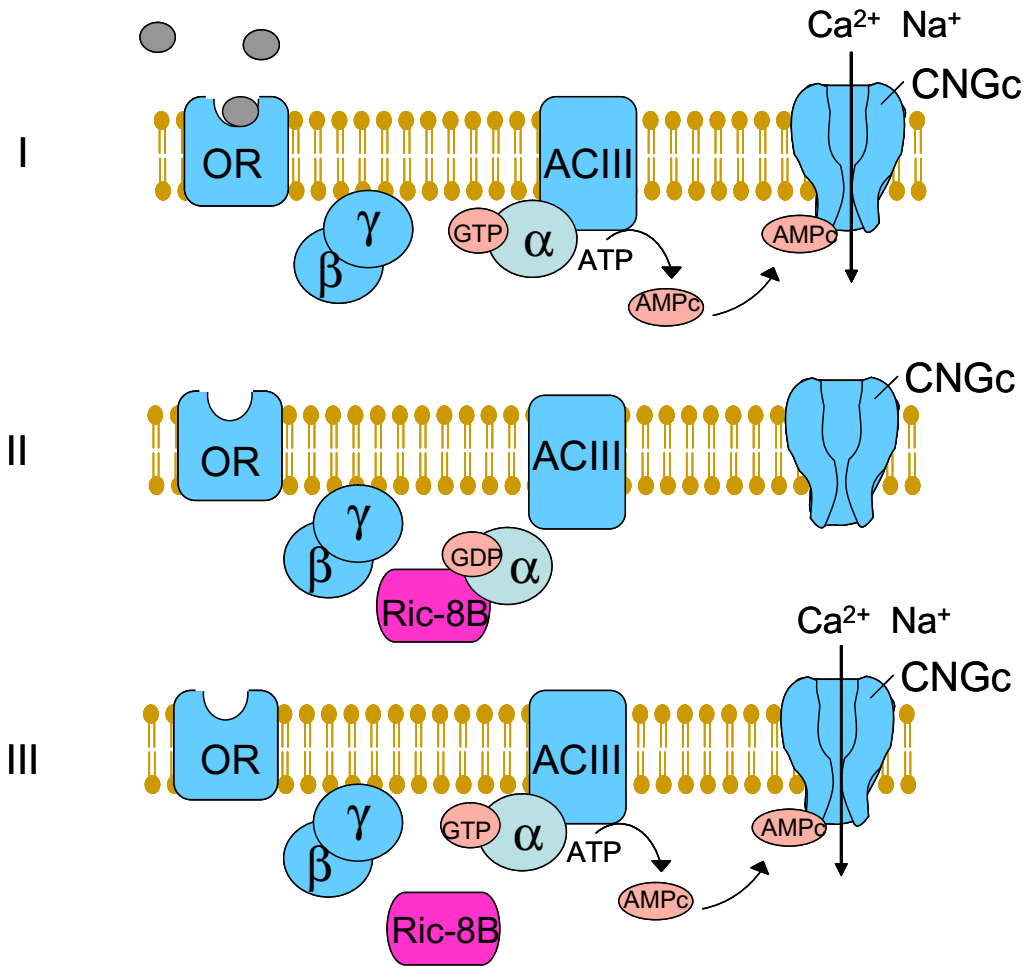

Figure 2. A possible role for Ric-8B, a putative Guanine nucleotide Exchange Factor (GEF), in odorant signal transduction. Once an OR is bound by its specific ligand, Gαolf is activated and released from the heterotrimeric G protein complex (I). The GTP bound Gαolf is now able to activate adenylyl cyclase III to produce cAMP, until the GTP is hydrolyzed to GDP. Before the GDP bound Gαolf is reassociated in a heterotrimeric complex, Ric-8B interacts with Gαolf (II) and catalyzes the exchange of GDP for GTP to regenerate the activated form of Gαolf (III), which is then able to further activate adenylyl cyclase III, producing increased amounts of cAMP. OR, odorant receptor; ACIII, adenylyl cyclase III; CNGc, cyclic nucleotide gated channel.

4. The Vomeronasal Receptor Signaling Pathways

The VR signaling pathway is not as well characterized as the one for ORs. Basically, ligand binding to V1Rs leads to activation of a G protein (likely subunit Gαi2) and release of Gβ/γ which in turn activates phospholipase C (PLC) to produce diacylglycerol (DAG) and inositol- 1, 4, 5- triphosphate (IP3). DAG activates TRP2 cation channel, leading to Ca^{2+} influx and depolarization of the neurons (Munger *et al.*, 2009). The involvement of the TRP2 cation channel in VR signal transduction is supported by studies that analyzed TRP2 knockout mice. These mice show impaired pheromone mediated behaviors, such as aggression and sexual behaviors (Leypold *et al.*, 2002; Stowers *et al.*, 2002; Kimchi *et al.*, 2007).

The signaling properties of the V2R expressing neurons are even less understood (Munger *et al.*, 2009). V2Rs are likely to couple to the Gαo protein, which ultimately results in increases in the intracellular Ca^{2+} concentration. The TRP2 channel is also expressed in the basal layer of the vomeronasal epithelium (Liman *et al.*, 1999), and is required for the activation of V2R expressing neurons by some ligands, such as the major urinary proteins (MUPs), highly polymorphic proteins present in urine which are involved in the regulation of aggressive behaviors (Chamero *et al.*, 2007). However, the recognition of the major histocompatibility complex (MHC) peptides, another known class of ligands for V2Rs, does not require a functional TRP2 channel (Kelliher *et al.*, 2006).

The complete set of proteins involved in V1R and V2R signaling still need to be determined. We have shown that Gγ13, a G protein subunit that is expressed in olfactory neurons and taste cells, is expressed in the apical, V1R expressing layer of the vomeronasal epithelium, but not in the basal layer (Kerr *et al.*, 2008). Whether Gγ13, is involved in V1R signal transduction remains to be determined.

5. Concluding Remarks

GPCRs constitute the largest family of surface molecules involved in signal transduction and are involved in an enormous number of biological functions. They are activated by a variety of ligands, which include hormones, growth factors, light, peptides, neurotransmitters, nucleotides, and aminoacids. In 1991, Buck and Axel (Buck & Axel, 1991) discovered that odorant receptors are GPCRs, and since then many other new GPCR families involved in olfaction as well as in other chemosensorial functions have been identified. These new families recognize different types of ligands such as pheromones, tastants, biogenic amines and formyl peptides. The characterization of the members of these chemosensorial GPCR families and their respective ligands should contribute to the understanding of different aspects of chemical communication in mammals.

6. References

Belluscio L, Gold GH, Nemes A, Axel R. Mice deficient in G(olf) are anosmic. Neuron 1998;20:69-81.

Blake B, Wing M, Zhou J, Lei Q, Hillmann J, Behe C, Morris R, Harden T, Bayliss D, Miller R, Siderovski D. Gb association and effector interaction selectivities of the divergent Gg subunit Gg13. J Biol Chem 2001;276:49267-74.

Boekhoff I, Breer H. Termination of second messenger signaling in olfaction. Proc Natl Acad Sci U S A 1992;89:471-4.

Boekhoff I, Tareilus E, Strotmann J, Breer H. Rapid activation of alternative second messenger pathways in olfactory cilia from rats by different odorants. Embo J 1990;9:2453-8.

Borisy F, Ronnet G, Cunningham A, Juilfs D, Beavo J, Snyder S. Calcium/calmodulin-activated phosphodiasterase expressed in olfactory receptor neurons. J. Neuroscience 1992;12:915-23.

Breer H, Boekhoff I, Tareilus E. Rapid kinetics of second messenger formation in olfactory transduction. Nature 1990;345:65-8.

Brennan P, Keverne E. Something in the air? New insights into mammalian pheromones. Current Biology 2004;14:R81-R89.

Brennan P, Zufall F. Pheromonal communication in vertebrates. Nature 2006;444:308-315.
Brunet LJ, Gold GH, Ngai J. General anosmia caused by a targeted disruption of the mouse olfactory cyclic nucleotide-gated cation channel. Neuron 1996;17:681-93.
Buck L. Information coding in the vertebrate olfactory system. Ann Rev Neurosci 1996;19:517-44.
Buck L, Axel R. A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. Cell 1991;65:175-87.
Chamero P, Marton TF, Logan DW, Flanagan K, Cruz JR, Saghatelian A, Cravatt BF, Stowers L. Identification of protein pheromones that promote aggressive behaviour. Nature 2007;450:899-902.
Chen TY, Yau KW. Direct modulation by Ca^{2+}-calmodulin of cyclic nucleotide-activated channel of rat olfactory receptor neurons. Nature 1994;368:545-8.
Del Punta K, Leinders-Zufall T, Rodriguez I, Jukam D, Wysocki C, Ogawa S, Zufall F, Mombaerts P. Deficient pheromone responses in mice lacking a cluster of vomeronasal receptor genes. Nature 2002;419:70-4.
Doving KB, Trotier D. Structure and function of the vomeronasal organ. J Exp Biol 1998;201:2913-25.
Dulac C, Torello AT. Molecular detection of pheromone signals in mammals: from genes to behaviour. Nat Reviews Neuroscience 2003;4:551-62.
Firestein S. How the olfactory system makes sense of scents. Nature 2001;413:211-8.
Glusman G, Yanai I, Rubin I, Lancet D. The complete human olfactory subgenome. Genome Res 2001;11:685-702.
Godfrey PA, Malnic B, Buck LB. The mouse olfactory receptor gene family. Proc Natl Acad Sci U S A 2004;101:2156-61.
Huang L, Shanker Y, Dubauskaite J, Zheng J, Yan W, Rosenzweig S, Spielman A, Max M, Margolskee R. Gg13 colocalizes with gustducin in taste receptor cells and mediates IP3 responses to bitter denatonium. Nat Neurosci 1999;2:1055-62.
Hudson R, Distel H. Pheromonal release of suckling in rabbits does not depend on the vomeronasal organ. Physiol Behav 1986;37:123-8.
Kelliher KR, Spehr M, Li XH, Zufall F, Leinders-Zufall T. Pheromonal recognition memory induced by TRPC2-independent vomeronasal sensing. Eur J Neurosci 2006;23:3385-90.
Kerr D, Von Dannecker L, Davalos M, Michaloski J, Malnic B. Ric-8B interacts with Gaolf and Gg13 and co-localizes with Gaolf, Gb1 and Gg13 in the cilia of olfactory sensory neurons. Mol Cell Neurosci 2008;38:341-8.
Kimchi T, Xu J, Dulac C. A functional circuit underlying male sexual behaviour in the female mouse brain. Nature 2007;448:1009-14.
Kurahashi T, Menini A. Mechanism of odorant adaptation in the olfactory receptor cell. Nature 1997;385:725-9.
Leinders-Zufall T, Lane AP, Puche AC, Ma W, Novotny MV, Shipley MT, Zufall F. Ultrasensitive pheromone detection by mammalian vomeronasal neurons. Nature 2000;405:792-6.
Leypold BG, Yu CR, Leinders-Zufall T, Kim MM, Zufall F, Axel R. Altered sexual and social behaviors in trp2 mutant mice. Proc Natl Acad Sci U S A 2002;99:6376-81.
Liberles S, Buck L. A second class of chemosensory receptors in the olfactory epithelium. Nature 2006;442:645-50.
Liman ER, Corey DP, Dulac C. TRP2: A candidate transduction channel for mammalian pheromone sensory signaling. Proc Natl Acad Sci USA 1999;96:5791-6.
Malnic B, Godfrey PA, Buck LB. The human olfactory receptor gene family. Proc Natl Acad Sci U S A 2004;101:2584-9.
Malnic B, Hirono J, Sato T, Buck LB. Combinatorial receptor codes for odors. Cell 1999;96:713-23.
Mandiyan V, Coats J, Shah N. Deficits in sexual and aggressive behaviors in Cnga2 mutant mice. Nature Neuroscience 2005;8:1637-8.
Mashukova A, Spehr M, Hatt H, Neuhaus EM. Beta-arrestin2-mediated internalization of mammalian odorant receptors. J Neurosci 2006;26:9902-12.
Migeotte I, Communi D, Parmentier M. Formyl peptide receptors: a promiscuous subfamily of G protein-coupled receptors controlling immune responses. Cytokine Growth Factor Rev 2006;17:501-19.

Mombaerts P. Genes and ligands for odorant, vomeronasal and taste receptors. Nat Reviews Neuroscience 2004;5:263-78.
Munger SD, Leinders-Zufall T, Zufall F. Subsystem Organization of the Mammalian Sense of Smell. Annu Rev Physiol 2009;71:115-40.
Munger SD, Lane AP, Zhong H, Leinders-Zufall T, Yau KW, Zufall F, Reed RR. Central role of the CNG4 channel subunit in Ca^{2+}-calmodulin-dependent odor adaptation. Science 2001;294:2172-5.
Niimura Y, Nei M. Evolution of olfactory receptor genes in the human genome. Proc Natl Acad Sci U S A 2003;100:12235-40.
Niimura Y, Nei M. Comparative evolutionary analysis of olfactory receptor genes clusters between humans and mice. Gene 2005;346:13-21.
Peppel K, Boekhoff I, McDonald P, Breer H, Caron MG, Lefkowitz RJ. G protein-coupled receptor kinase 3 (GRK3) gene disruption leads to loss of odorant receptor desensitization. J Biol Chem 1997;272:25425-8.
Ressler KJ, Sullivan SL, Buck LB. A zonal organization of odorant receptor gene expression in the olfactory epithelium. Cell 1993;73:597-609.
Ressler KJ, Sullivan SL, Buck LB. Information coding in the olfactory system: evidence for a stereotyped and highly organized epitope map in the olfactory bulb. Cell 1994;79:1245-55.
Riviere S, Challet L, Fluegge D, Spehr M, Rodriguez I. Formyl peptide receptor-like proteins are a novel family of vomeronasal chemosensors. Nature 2009;459(7246):547-77.
Rodriguez I, Mombaerts P. Novel human vomeronasal receptor-like genes reveal species-specific families. Curr Biol 2002;12:R409-11.
Rodriguez I, Greer CA, Mok MY, Mombaerts P. A putative pheromone receptor gene expressed in human olfactory mucosa. Nature Genetics 2000;26:1-2.
Rodriguez I, Del Punta K, Rothman A, Ishii T, Mombaerts P. Multiple new and isolated families within the mouse superfamily of V1r vomeronasal receptors. Nature Neuroscience 2002;5:134-40.
Ronnett GV, Moon C. G proteins and olfactory signal transduction. Annu Rev Physiol 2002;64:189-222.
Sam M, Vora S, Malnic B, Ma W, Novotny MV, Buck LB. Odorants may arouse instinctive behaviours. Nature 2001;412:142.
Shi P, Zhang J. Comparative genomic analysis identifies an evolutionary shift of vomeronasal gene repertoires in the vertebrate transition from water to land. Genome Research 2007;17:166-74.
Sinnarajah S, Dessauer CW, Srikumar D, Chen J, Yuen J, Yilma S, Dennis JC, Morrison EE, Vodyanoy V, Kehrl JH. RGS2 regulates signal transduction in olfactory neurons by attenuating activation of adenylyl cyclase III. Nature 2001;409:1051-5.
Spehr M, Kelliher KR, Li XH, Boehm T, Leinders-Zufall T, Zufall F. Essential role of the main olfactory system in social recognition of major histocompatibility complex peptide ligands. J Neurosci 2006;26:1961-70.
Stowers L, Holy TE, Meister M, Dulac C, Koentges G. Loss of sex discrimination and male-male aggression in mice deficient for TRP2. Science 2002;295:1493-1500.
Touhara K. Molecular biology of peptide pheromone production and reception in mice. Adv Genet 2007;59:147-71.
Vassar R, Ngai J, Axel R. Spatial segregation of odorant receptor expression in the mammalian olfactory epithelium. Cell 1993;74:309-18.
Vassar R, Chao S, Sitcheran R, Nunez J, Vosshall L, Axel R. Topographic organization of sensory projections to the olfactory bulb. Cell 1994;79:981-91.
Von Dannecker L, Mercadante A, Malnic B. Ric-8B, an olfactory putative GTP exchange factor, amplifies signal transduction through the olfactory-specific G-protein Gaolf. J Neurosci 2005;25:3793-3800.
Von Dannecker L, Mercadante A, Malnic B. Ric-8B promotes functional expression of odorant receptors. Proc Natl Acad Sci U S A 2006;103:9310-4.
Wei J, Zhao AZ, Chan GCK, Baker LP, Impey S, Beavo JA, Storm DR. Phosphorylation and inhibition of olfactory adenylyl cyclase by CaM kinase II in neurons: a mechanism for attenuation of olfactory signals. Neuron 1998;21:495-504.

Wong ST, Trinh K, Hacker B, Chan GCK, Lowe G, Gaggar A, Xia Z, Gold GH, Storm DR. Disruption of the type III adenylyl cyclase gene leads to peripheral and behavioral anosmia in transgenic mice. Neuron 2000;27:487-97.

Xu F, Schaefer M, Kida I, Schafer J, Liu N, Rothman DL, Hyder F, Restrepo D, Shepherd GM. Simultaneous activation of mouse main and accessory olfactory bulbs by odors or pheromones. J Comp Neurol 2005;489:491-500.

Yan C, Zhao AZ, Bentley JK, Loughney K, Ferguson K, Beavo JA. Molecular cloning and characterization of a calmodulin-dependent phosphodiesterase enriched in olfactory sensory neurons. Proc Natl Acad Sci U S A 1995;92:9677-81.

Young J, Trask B. V2R gene families degenerated in primates, dog and cow, but expanded in opossum. Trends in Genetics 2007;23:212-15.

Young J, Kambere M, Trask B, Lane R. Divergent V1R repertoires in five species: Amplification in rodents, decimation in primates, and a surprisingly small repertoire in dogs. Genome Research 2005;15:231-40.

Young JM, C. F, Williams EM, Ross JA, Tonnes-Priddy L, Trask BJ. Different evolutionary processes shaped the mouse and human olfactory receptor gene families. Hum Mol Genet 2002;11:535-46.

Zhang X, Rodriguez I, Mombaerts P, Firestein S. Odorant and vomeronasal receptor genes in two mouse genome assemblies. Genomics 2004;83:802-11.

Zheng C, Feinstein P, Bozza T, Rodriguez I, Mombaerts P. Peripheral olfactory projections are differentially affected in mice deficient in a cyclic nucleotide-gated channel subunit. Neuron 2000;26:81-91.

Zozulya S, Echeverri F, Nguyen T. The human olfactory receptor repertoire. Genome Biology 2001;2:18.11-18.12.