30. Olfactory Subsystems

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A plethora of structurally diverse environmental chemosignals convey critical information for survival, health, and reproduction. To meet the bewildering structural complexity of the chemical *odor space*, distinct cellular mechanisms and, ultimately, sensory subsystems have evolved to detect and discriminate these varied chemostimuli. Mammalian olfactory subsystems can be categorized by the stimuli they detect, the signaling proteins they express, and the central circuits that process these information. This chapter is centered on noncanonical olfactory subsystems and their peripheral sensory structures – the vomeronasal organ, the septal organ of Masera, and the Grüneberg ganglion.

Animals, including humans, detect and respond to a plethora of structurally diverse environmental chemical cues. These chemosignals convey critical information for survival, health, and reproduction:

- Food type and quality
- The existence (and concentration) of toxins
- The presence of prey, predators, competitors, or potential mates
- Social cues that elicit stereotyped, genetically preprogrammed behaviors or hormonal responses.

To meet the bewildering structural complexity of the chemical *odor space*, distinct molecular and cellular mechanisms have evolved to detect and discriminate these varied stimuli [30.1, 2].

In recent years, it has become increasingly clear that the mammalian olfactory system is organized into multiple subsystems that can be categorized by the chemostimuli to which they respond, the receptors and downstream signaling proteins they express, and the brain circuits that process these information [30.3–6]. The diversity of olfactory subsystems manifests both in the occurrence of anatomically distinct chemosensory structures within the mammalian nose and in the coexistence of unique neuronal subpopulations within individual tissue(s).

In the following, this chapter will focus on the noncanonical chemosensory subsystems that, in part, have only recently (re)gained scientific attention. The majority of experimental research on olfactory subsystems has been carried out in mice. As their genetic amenability allows integrated investigations that span the molecular, cellular, and systems level [30.7], the findings presented below are largely restricted to this model organism.

30.1 The Subsystem Organization of the Sense of Smell

At least four different chemosensory structures are found in the rodent nose (Fig. 30.1):

1. The main olfactory epithelium (MOE)
2. The septal organ (SO) of Masera

3. The vomeronasal organ (VNO)
4. The Grüneberg ganglion (GG).

The newfound appreciation of an organizational concept of olfactory subsystems – or noses within noses [30.8] – comes with the recognition of profound differences in the molecular and cellular mechanisms that, at least theoretically, confer a substantial degree of stimulus selectivity for each subsystem and, thus, allow dedication of each structure to a particular role in chemosensation [30.9]. The high level of specialization perhaps becomes most apparent when considering the rapidly expanding repertoire of chemosensory receptor gene/protein families employed by the different systems. While the majority of putative chemoreceptor genes encode for members of the *classical* odorant receptor [30.10] gene family – which, in most mammals, accounts for as much as 2% of the whole genome – noncanonical chemosensory genes devoted to encoding the proteins of smell also make up a significant proportion of many genomes [30.11, 12]. This clear indication of the importance of the sense of smell and its underlying olfactory (sub)systems contrasts our, at present, still largely fragmentary conception of sensory signaling in many noncanonical olfactory cells and tissues.

Not too long ago, it was widely accepted that the mammalian olfactory system had only two anatomical and functional divisions: a main and an accessory (vomeronasal) olfactory system [30.9, 13]. In the 1970s, anatomical description of segregated parallel projections of the main and accessory systems to different *telencephalic* and *diencephalic* nuclei then founded the dual olfactory hypothesis [30.14]. Accordingly, the main system was believed to predominantly detect general environmental odor cues, whereas the accessory system and its peripheral sensory structure – the VNO – were considered to serve a crucial function in the detection and communication of social chemosignals that elicit stereotyped social and sexual behaviors and/or hormonal responses among conspecific animals [30.14, 15]. These two divisions of the olfactory system are by no means homogeneous [30.1]. The MOE contains various sensory neuron subpopulations that respond to distinct classes of chemostimuli, express different receptors – both *Gprotein-coupled receptors* (GPCRs) as well as non-GPCRs – and utilize a variety of transduction pathways. Similarly, the VNO contains at least three different groups of neurons that also vary in stimulus selectivity and transduction mechanisms.

As it has now become apparent that the organization of the sense of smell does not adhere to a strict anatomical and functional dichotomy, but is rather much more complex, several exciting questions now rank high on the agenda of (chemo)sensory neurobiologists:

1. Which receptor structures and signaling strategies are implemented by each different sensory tissue/cell population?
2. What coding logic underpins the anatomical segregation of the different subsystems in the nasal cavity?
3. How is subsystem-specific parallel information routed to and integrated by higher order circuits?
4. What is the exact role that each subsystem plays in regulating chemosensory-dependent behaviors?

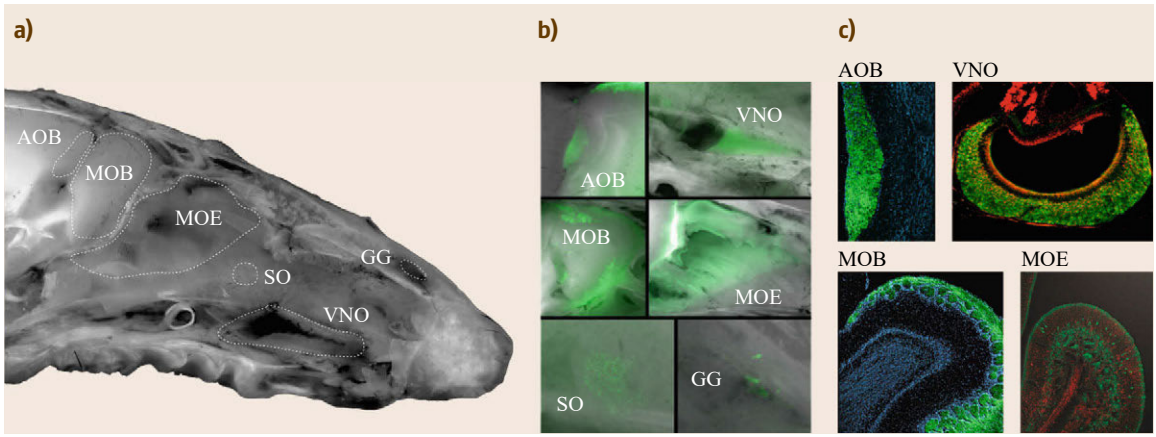

Fig. 30.1a–c Subsystem organization of the sense of smell. **(a)** Para-sagittal hemisection of the rostral head of a mouse that expresses the green fluorescent protein under transcriptional control of the olfactory marker protein promotor. **(b)** Merged *en-face* images under brightfield and epi-fluorescence illumination illustrate the different olfactory subsystems as well as their primary central projection areas. **(c)** Cryosections reveal GFP fluorescence of olfactory tissues: Grüneberg ganglion (GG), VNO, septal organ (SO), main olfactory epithelium (MOE), main olfactory bulb (MOB), accessory olfactory bulb (AOB)

30.2 The Vomeronasal System

In 1813, the Danish anatomist Ludvig L. Jacobson described a novel mammalian organ *located in the foremost part of the nasal cavity, in close contact with the septum, on palatal elongations of the intermaxillary bone* [30.16]. He concluded from comparative investigations in various species that *the organ exists in all mammals* and most likely functions as a *sensory organ which may be of assistance to the sense of smell* [30.16]. Originally designated as the *organ of Jacobson*, this enigmatic structure was (re)named in 1895 *organon vomeronasale* (*Jacobsoni*) or *VNO*.

The VNO is a bilaterally symmetrical paired tubular structure at the base of the anterior nasal septum, located just above the palate [30.17, 18] (Fig. 30.1). Enclosed in a bony capsule, the blind-ended organ opens anteriorly into either the oral or the nasal cavity via the nasopalatine or vomeronasal duct, depending on the species examined. Viscous lateral gland secretions fill the VNO lumen [30.1] which separates a medial crescent-shaped pseudo-stratified sensory neuroepithelium from lateral cavernous tissue that harbors a large blood vessel that is extensively innervated by nerve fibers from the superior cervical ganglion [30.19, 20]. The sensory epithelium is mainly composed of basal cells, sustentacular cells, and mature *vomeronasal sensory neurons* (VSNs). The small bipolar VSNs each extend an unbranched apical dendrite that ends in a microvillous swelling (*knob*) at the epithelial surface. At the basal soma, VSNs extend single unbranched axons that gather into nerve bundles that project below the septal epithelium, dorsally pass the cribriform plate, and project along the olfactory bulb's medial sides to the glomerular layer of the *accessory olfactory bulb* (AOB) [30.18]. The mouse VNO consists of a few hundred thousand VSNs in total [30.21]. Each neuron gains structural and metabolic support from sustentacular cells in the most superficial epithelial layer. Even in aged animals, VSNs are continuously replaced from a vomeronasal pool of adult pluripotent cells [30.22] that are located along the basal epithelial membrane as well as in the marginal zones [30.17].

How is VNO stimulus uptake achieved? In situations of stress and/or novelty-induced arousal, sympathetic activity triggers adrenergic release and, consequently, a peristaltic vascular pumping mechanism causes massive fluid entry into the VNO. This way, following direct contact with urine deposits, vaginal secretions, facial gland secretions or saliva, relatively nonvolatile stimuli, such as peptides or proteins gain access to the VNO lumen [30.23, 24].

Initially observed between embryonic days 12 and 13 in the rat [30.25], the vomeronasal neuroepithelium is embryologically derived from an *olfactory placode* evagination. As assessed by expression of the olfactory marker protein (OMP), mouse VSNs are first identified by embryonic day 14 [30.26]. The lateral vascular pattern is completed later in prenatal *ontogeny*, around embryonic day 18 [30.27]. At this stage, the vomeronasal nerve appears fully developed. While all structural vomeronasal components thus seem present at birth [30.28], VNO function in neonates and juveniles is still debated [30.29–31].

30.2.1 Molecular and Cellular Mechanisms of Vomeronasal Signaling

Vomeronasal Chemoreceptors

In most mammalian species, the VNO displays both a structural and functional dichotomy [30.31–33]. At least two topographically segregated neuronal subpopulations express distinct repertoires of receptors and other putative signaling molecules [30.34–36]. In the sensory epithelium's apical layer, VSNs express the G protein α-subunit $G_{\alpha i2}$ together with phosphodiesterase 4A (PDE4A) and a member of a multigene family that encodes class-A (rhodopsin-like) GPCRs: the V1Rs [30.37–39]. Vomeronasal receptor types 1 (V1R) appear exclusively expressed in the VNO [30.38] in a punctate, nonoverlapping pattern. The murine *V1r* gene family contains more than 150 potentially functional members and a similar number of pseudogenes [30.39, 40]. These genes are highly divergent and polymorphic. They share intron-free open reading frames that are found on most chromosomes in a clustered organization [30.40, 41]. Each of the 12 relatively isolated *V1r* families contains between 1 and 30 members [30.39, 42]. In a given VSN, *V1r* gene choice is tightly controlled. *Monoallelic expression* results in a distinct V1R chemodetector *morph* for each neuron [30.43] ensuring that individual VSNs obtain a unique functional identity. *Gene cluster* deletion of all (but one) *V1r*a and *V1r*b family members has shown that VSN chemoresponsivity critically depends on at least some V1Rs [30.44]. To date, however, the majority of *V1r* genes products remain *orphan receptors*. Remarkably, Catherine Dulac and coworkers recently determined sensitivity of ≈ 50 individual V1Rs to a variety of ethologically relevant cues [30.45]. Their data reveal that individual *V1r* subfamilies could have evolved toward the recognition of specific groups of animals or behaviorally relevant chemical structures.

The molecular mechanisms underlying monoallelic gene choice – a hallmark of *V1r* expression [30.40, 43, 46] – remain elusive. The interrupted cluster organiza-

tion of many *V1r* genes may not just reflect multiple gene-duplication events, but may also allow choice regulation to function at the cluster level [30.40]. As shown for mutually exclusive OR gene choice [30.47, 48], transcription of a nonfunctional *V1r* allele triggers coexpression of a second, functional *V1r* gene. This, in turn, then drives a negative feedback mechanism that maintains monoallelic expression. Remarkably, this negative feedback is also maintained when an exogenous OR gene is expressed from a *V1r* locus [30.41]. This surprising finding suggests a common mechanism of monoallelic chemoreceptor transcription in both olfactory sensory neurons (OSN) and VSNs.

A molecularly distinct population of neurons forms the basal VNO layer. Basal VSNs express $G_{\alpha o}$ and members V2R family of GPCRs [30.49–51]. Approximately 120 intact *V2r* genes are found in the mouse genome, whereas an additional ≈ 160 appear pseudogenized [30.52]. Members of the V2R family are typical class-C GPCRs that share a large hydrophobic N-terminal extracellular domain. This extracellular *venus flytrap* module has been attributed to function as the primary site of ligand binding [30.12]. While there is no apparent sequence homology with *V1r* genes, *V2r* gene family members are distantly related to metabotropic glutamate receptors, Ca^{2+}-sensing receptors, metabotropic glutamate receptors, and *T1r* taste receptors [30.12, 32]. Like the *V1r*s, *V2r* genes are mostly organized in clusters on many chromosomes. Based on sequence homology, four distinct *V2r* families are distinguished: family-A, -B, and -D, as well as family-C (a.k.a. *V2r2*) [30.52–55]. With more than 100 members, the vast majority of *V2r*s are family-A genes. By contrast, only four genes constitute family-D. With the exception of family-C receptors, mutually exclusive monoallelic transcription of *V2r* genes underlies a punctate expression pattern. By contrast, family-C receptors do not *obey* the chemosensory *one neuron – one receptor* rule [30.1, 5]. The seven highly homologous (> 80%) family-C proteins are found in most, if not all, $G_{\alpha o}$-positive VSNs [30.53]. Somewhat reminiscent of the atypical insect olfactory coreceptor Orco [30.56], this rather unusual coexpression of family-C *V2r* genes in basal VSNs could indicate chaperoning and/or dimerization function. Whether this holds true, however, remains to be determined [30.2].

H2-Mv (or *M10*) genes are members of a family of nine nonclassical class Ib *major histocompatibility complex* (MHC) genes that, as concurrently reported by two groups in 2003 [30.36, 57], are expressed by V2R-positive basal VSNs. Initially, H2-Mv proteins were believed to associate with V2Rs and, together with β2-microglobulin, serve as essential chaperones for V2R trafficking and surface expression [30.32, 36]. However, a considerable fraction of basal VSNs lacks *H2-Mv* gene expression [30.34] and while the *H2-Mv* family is exclusively found in rodents, other mammals such as the opossum express putatively functional *V2r* genes without intact *H2-Mv* genes [30.52, 58]. Moreover, a recent study suggests that H2-Mv proteins, while not absolutely essential for the generation of physiological responses, are required for ultrasensitive chemodetection by a subset of VSNs [30.35].

As for *V1r*s, gene deletion studies have provided direct evidence that at least some V2Rs mediate VSN chemosignals. Knockout of the *Vmn2r26* (*V2r1b*) or *Vmn2r116* (*V2rp5*) genes results in drastically diminished VSN sensitivity to the male-specific exocrine gland-secreting peptide 1 (ESP1 [30.59]) or MHC class I peptide ligands [30.60], respectively. Both stimuli, however, trigger highly sensitive VSN responses in wildtype mice.

With the notable exception of a recent study that reported promising advances in recombinant V2R plasma membrane targeting [30.61], V1R/V2R *deorphanization* attempts in *heterologous expression* systems have largely failed. We still lack a mechanistic understanding of V1R/V2R cell-surface expression.

In 2009, two groups identified a third family of five putative VNO chemoreceptors [30.62, 63]. These candidate chemosensory GPCR-encoding genes are all members of the formyl peptide receptor (FPR)-like gene family (*Fpr-rs1*, *rs3*, *rs4*, *rs6*, and *rs7*). Their predicted seven-transmembrane topology, their selective, punctate and *monogenic* vomeronasal expression pattern, and their localization in microvillous dendritic VSN endings [30.62, 63] strongly suggest a functional role of FPR-like receptors in vomeronasal chemosignaling. Interestingly, while *Fpr-rs1* is coexpressed with $G_{\alpha o}$ in basal sensory neurons, the remaining vomeronasal *Fpr-rs* genes all coexpress with $G_{\alpha i2}$ in the apical layer of the VNO neuroepithelium [30.8].

The two prototypical FPRs, FPR1 and FPR-rs2, are known for their function in immune cells, such as neutrophils and monocytes [30.64]. Here, both receptors serve crucial functions in host defense against pathogens [30.65]. A characteristic of immune system FPRs is their ligand promiscuity; a wide range of compounds are detected and function as leucocyte chemoattractants that signal direction toward sites of infection or tissue damage. Mitochondrially encoded peptides, the formylated bacterial peptide *N*-formylmethionine-leucine-phenylalanine (fMLF), and various other antimicrobial/inflammatory modulators activate immune system FPRs [30.66], suggesting functionally, rather than structurally defined ligand spectra. Interestingly, neither FPR1 nor FPR-rs2 was found transcribed in VSNs [30.62, 63].

Neither V1/2Rs nor ORs share significant sequence homology with immune system *Fpr*s or vomeronasal *Fpr-rs* genes. Liberles and coworkers suggested that vomeronasal *Fpr*s evolved from several recent gene duplications and positive Darwinian selection in the rodent lineage [30.62] since the single *Fpr-rs* gene cluster is directly adjacent to a stretch of more than 30 *V1/2r* genes. Together with recent functional data obtained from recombinant FPR expression [30.67], these theoretical considerations argue for neofunctionalization of vomeronasal *Fpr* genes. By contrast, VSNs are activated in situ by fMLF as well as the mitochondria-derived formylated peptides [30.68] and heterologously expressed FPR-rs proteins retain agonist spectra that share some similarities to immune system FPRs [30.63]. As true for most vomeronasal chemoreceptors, the exact biological role of vomeronasal FPRs remains to be determined.

Signaling Cascade(s) and General VSN Physiology

Gaining detailed conceptual insight into the transduction mechanisms downstream V1R, V2R, or FPR-rs receptor activation is central to understanding how chemosignals control social and sexual behavior. So far, translation of the chemical binding energy between any VNO receptor and its cognate ligand into a meaningful electrical signal that can be read out by the brain is only partly understood and many critical aspects of VSN physiology are yet to be revealed. Upon exposure to natural sources of semiochemicals such as urine, vaginal secretions, or saliva, VSNs depolarize, display an increased action potential firing rate and, consequently, a transient increase in cytosolic Ca^{2+} [30.62, 69–80]. A physiological hallmark of VSNs is their extraordinarily high *input resistance* of typically several gigaohms [30.81–84]. Consequently, receptor current amplitudes of only a few picoamperes generate robust trains of *action potentials*. This passive membrane property contributes considerably to the exquisitely high electrical sensitivity of VSNs, rendering vomeronasal neurons among the most sensitive sensory structures.

In addition to *conventional* Hodgkin-Huxley type voltage-dependent conductances, such as *TTX*-sensitive Na^+ and delayed rectifier K^+ currents [30.85], several other ion channels shape the electrophysiological input-output function of VSNs. Action potential discharge is, in part, driven by *L*- and *T*-type Ca_v^{2+} currents that generate low-threshold Ca^{2+} spikes [30.82, 84]. Moreover, functional coupling of these Ca_v^{2+} currents to large-conductance Ca^{2+}-sensitive K^+ (BK) channels was proposed to maintain persistent spiking [30.84]. By contrast, a similar coupling mechanism was suggested to underlie sensory adaptation via arachidonic acid-dependent BK channel recruitment during stimulation [30.86]. Another K^+ channel, the ether-á-go-go-related (ERG) K^+ channel, is expressed in a layer-specific and activity-dependent manner, serving a homeostatic function by controlling the output characteristics of basal VSNs [30.9, 81]. ERG channel expression is poised to adjust VSNs to a target output range in a use-dependent manner, thus, extending the dynamic range of the neurons' stimulus – response function. In addition, hyperpolarization-dependent I_h currents are yet another voltage-gated conductance that shapes VSN excitability [30.87].

Ever since the initial reports on layer-specific $G_{\alpha i2}$ and $G_{\alpha o}$ coexpression in dendritic tips of V1R- and V2R-positive VSNs, respectively [30.37, 88, 89], speculation thrived on the notion of a functional role of either G protein α-subunit in apical and basal signaling pathways, respectively. While being an attractive model, conclusive evidence in favor of this concept was only recently reported. *Chamero* and coworkers demonstrated an essential requirement of $G_{\alpha o}$ in VSN responses to MHC I antigens, MUPs, mitochondrially encoded FPR-rs1 ligands, as well as ESP1 [30.68]. However, neuronal responses to fMLF, a stimulus shown to activate at least some of the four $G_{\alpha i2}$-coupled FPRs [30.63], were unaltered in $G_{\alpha o}$-deficient mice [30.68]. Similar studies supporting a role of $G_{\alpha i2}$ in V1R-mediated signaling are currently lacking. As expected for unconditional knockout of abundantly and promiscuous signaling proteins such as $G_{\alpha i2}$ and $G_{\alpha o}$, constitutive gene deletion models are likely to bear a range of phenotypic defects. Accordingly, global $G_{\alpha i2}$ and $G_{\alpha o}$ deletions did not allow a clearly VNO-dependent phenotype to be unambiguously attributed [30.90, 91].

Despite the fact that genetic deletion studies are also lacking, greater consensus is achieved on a critical function of phospholipase C (PLC) in vomeronasal signal transduction [30.13]. PLC activity promotes turnover of phosphatidylinositol-4,5-bisphosphate (PIP_2), resulting in elevated concentrations of the soluble messenger molecule inositol-1,4,5-trisphosphate (IP_3) and membrane-bound diacylglycerol (DAG). While DAG either directly targets membrane proteins or is metabolized to tertiary polyunsaturated fatty acid signals, IP_3 triggers massive Ca^{2+} release from intracellular storage organelles. Over the years, different functions for either or all products of PLC-dependent lipid turnover have been proposed [30.73, 77, 80, 92, 93]. The common denominator of all such models is both a central role of cytosolic Ca^{2+} elevations and an important, though not indispensable function of the *transient receptor potential (TRP) channel* TRPC2 [30.94] that

is abundantly expressed in VNO sensory microvilli. Without a doubt, *TrpC2*$^{-/-}$ mice display severe defects in various social and sexual behaviors [30.95, 96]. There are, however, phenotypic differences when *TrpC2* deletion models are compared to surgical VNO ablation [30.97, 98]. Moreover, evidence for (residual) urine-evoked activity in *TrpC2*$^{-/-}$ VSNs is accumulating [30.73, 93, 97], adding another layer of complexity to our current concept of vomeronasal signaling. Interestingly, a recent study documents two previously unrecognized types of *Trpc2*$^{+}$ neurons in the MOE of mice of various ages, thus, challenging the conventional VNO-centric interpretation of the behavioral phenotypes of *Trpc2* knockout mice.

A variety of signaling cascade proteins are, either directly or indirectly, subject to Ca^{2+}-dependent modulation. Therefore, transient or sustained cytosolic Ca^{2+} elevation, resulting from either TRPC2-dependent influx [30.77] and/or IP_3-mediated store depletion [30.73, 93], exerts both negative and positive feedback regulation in VSNs [30.7]. VSN sensory adaptation and gain control was shown to depend on down-regulation of TRPC2 by Ca^{2+}/calmodulin [30.99]. By contrast, a substantial portion of stimulus-evoked vomeronasal activity seems to be carried by a Ca^{2+} -activated chloride current (I_{Cl}) [30.73, 92, 93], resembling OSN transduction mechanisms [30.100, 101]. Vomeronasal I_{Cl} might be mediated by members of the *anoctamin* family of Ca^{2+} -activated chloride channels [30.102–104]. Microvillar colocalization with TRPC2 suggests that either anoctamin1 or anoctamin2, or both, could represent the vomeronasal Ca^{2+}-activated chloride channel(s) [30.92, 105–107]. However, caution should be exerted when interpreting signaling cascade similarities between VSNs and OSNs. Whether I_{Cl}, analogous to OSNs, contributes to depolarization or, by contrast, induces membrane hyperpolarization depends solely on the chloride equilibrium potential at the VSN microvillar membrane in vivo. This physiological parameter, however, is currently unknown.

30.2.2 Anatomy of the Accessory Olfactory System

Compared to many other sensory systems, both the anatomy and function of VNO-dependent neural circuits is poorly investigated. In general, sensory information in mammals is primarily processed by cortical neurons that allow for associative learning and enable a plastic stimulus response, both within and across individuals. By contrast, semiochemical-dependent behavior seems invariant and highly conserved among individuals. Accordingly, the VNO primarily activates noncortical circuits. Specifically, semiochemicals predominantly activate limbic networks that utilize more hardwired mechanisms than the cortex [30.14, 18]. Furthermore, vomeronasal stimulus processing is considered to follow a relatively *simple* logic. Between sensory input and output command, the circuits activated by VNO stimulation consist of three primary processing relays: the AOB, *amygdala*, and *hypothalamus* [30.108]. Whether and, if so, how circuit processing of vomeronasal stimuli is controlled by modulatory feedback mechanisms remains to be determined.

The Accessory Olfactory Bulb

After they passed through the *cribriform plate*, VSN axon bundles target the AOB, a distinct region at the dorso-caudal end of the olfactory bulb (Fig. 30.1). The two functional subsets of VSN axons project into two distinct AOB regions, thus, maintaining the anatomical dichotomy of the accessory olfactory system [30.7]. Apical V1R-positive neurons express the olfactory cell adhesion molecule (OCAM) but project to OCAM-negative second-order output neurons, mitral cells, in the rostral AOB, whereas basal V2R-positive VSNs lack OCAM expression and synapse with OCAM-positive mitral cells in the caudal AOB [30.109, 110]. Similar inverse OCAM expression has been reported in subsets of OSN axons and main bulb mitral/tufted cells [30.111].

VSNs with a distinct vomeronasal receptor (VR) chemodetector *morph* [30.43] converge onto mitral cell dendrites in 6–10 *glomeruli* that are scattered across broad AOB regions, but restricted to either the rostral or caudal part depending on receptor identity [30.112]. While some glomeruli appear exclusively innervated by neurons of a single VR *morph* [30.112], others were found to coalesce with different, but closely related, VSN axons [30.113]. While the jury is still out on the exact organizational rules that govern VSN-to-mitral cell connectivity in the AOB, the general glomerular organization likely serves to integrate incoming sensory information [30.43, 46].

As correctly noted by *Dulac* and *Wagner*, most basic properties of AOB biology remain almost unexplored. Thus, functional analogies with described main bulb circuitry is mostly speculative [30.114]. Unfortunately, premature extrapolation of anatomical principles and physiological mechanisms from the main to the AOB has seriously hampered an unbiased assessment of AOB neurobiology. Already in 1901, Ramon y Cajal pointed out several fundamental differences between the main to the accessory bulb [30.115]:

1. AOB glomeruli are relatively small, rather confluent and less defined.

2. The *external plexifom layer* in the AOB is, at best, rudimentary.
3. Projecting neuron somata in the AOB are rarely mitral shaped.

Conventional plexifom layers are, in fact, largely missing [30.116]. Instead, an internal and external cellular layer are separated by fiber bundles of the lateral olfactory tract [30.115]. Furthermore, AOB glomeruli are indeed small, though highly variable in size (10–30 µm diameter [30.117]). They are tightly clustered, surrounded by only a few periglomerular cells and innervated by a few hundred glutamatergic VSN axons terminals [30.118].

To date, two basic mitral cell connectivity models for glomerular information processing are discussed. The homotypic connectivity model suggests exclusive targeting of glomeruli that are innervated by VSN populations that share a VR *morph*, effectively rendering a divergent pattern of sensory axonal projections convergent by second-order AOB neurons [30.30, 112]. According to the heterotypic wiring scheme, mitral cell primary dendrites specifically target glomeruli that are innervated by VSNs expressing receptors of the same subfamily [30.113]; thus forming a glomerular map of subfamily-specific domains [30.114].

While lacking an extensive lateral dendritic tree, AOB mitral cells elaborate extensively branched primary dendrites. These dendrites terminate as multiple tufts in up to 12 different glomeruli [30.19, 113, 119–121] although the tufts' size and shape are anything but uniform. Interestingly, local regenerative *tuft spikes* were observed independently of somatic spikes, suggesting modes of local nonlinear synaptic input integration [30.121]. In addition, dendritic transmitter release in response to both subthreshold and suprathreshold excitation [30.122] as well as active backpropagation of sodium spikes from the soma [30.123] increase the computational power of individual mitral cells within the AOB network. Considering their output, AOB mitral cells are relatively slow with maximum firing frequencies < 50 Hz [30.124]. While this upper limit somewhat restricts the dynamic output range, the high density of axon collaterals that project to both the anterior and posterior AOB [30.115] ensures that activity will be transmitted throughout the network, providing an ideal circuit for synchronized output.

Similar to the main olfactory bulb, GABAergic granule cells build the main type of AOB *interneurons* [30.125]. They form synapses with mitral cells both within the glomerular layer and along proximal parts of mitral cell primary dendrites [30.126].

While thoroughly analyzed in the main olfactory bulb [30.127, 128], the reciprocal *dendrodendritic synapse* in the AOB has received considerably less attention [30.129–131]. Located along the basal segments of mitral cell dendrites, dendrodendritic AOB synapses primarily seem to provide relay-like recursive self-inhibitory feedback which sharpens *projection neuron* response selectivity [30.132] and might, thus, function as a sensory *gate* during learning and olfactory memory formation [30.129, 133–135].

30.2.3 Pheromones

Pheromones (*pherin* = to transfer and *hormone* = to excite), per definition, are conspecific chemosignals that elicit a specialized behavior or neuroendocrine response upon detection by members of the same species [30.136]. When the term was coined, Karlson and Lüscher most likely did not foresee that more than 50 years later there would still be a lively and controversial debate about the biological role and even the existence of pheromones [30.137–139]. Concerning the vomeronasal system, it is clear that VSNs detect ethologically relevant odors that other animals emit. These include pheromones and other semiochemicals as well as *kairomones*, heterospecific ligands that upon detection convey an ethological benefit to the receiver. In addition, in vitro studies also showed VSN responses to odors of unknown biological function that are not secreted by other animals [30.7, 140, 141].

While the chemical identity of vomeronasal stimuli, to a large extend, remains to be uncovered, different putative semiochemicals have been identified and can be roughly categorized as follows:

1. Major urinary proteins (MUPs)
2. MHC class I peptide ligands
3. Exocrine gland-secreting peptides (ESPs)
4. Sulfated steroids
5. Formylated peptides
6. Volatile small molecules.

MUPs, MHCs, and ESPs are peptides/small proteins that evolved by species-specific gene duplication events in the rodent lineage [30.142, 143]. For members of each peptide/protein class recognition by basal V2R-positive VSNs has been reported [30.69, 76, 142, 144, 145]. Sulfated steroids and other secreted small molecules appear to signal state- or gender-specific internal physiology [30.78, 146]. These stimuli are predominantly detected by apical neurons expressing members of the V1R receptor family [30.75, 147]. Formylated peptides as well as other pro- or anti-inflammatory disease-associated compounds were proposed to activate FPR-rs receptors [30.63]. In-

deed, these ligands activate both apical and basal VSNs [30.68].

Twenty-one species-specific genes constitute the mouse MUP family [30.143, 148]. MUPs are produced in the liver in a testosterone- and growth hormone-dependent manner primarily by adult males [30.149, 150]. As members of the lipocalin protein family, MUPs fold into a β-barrel that creates an internal binding pocket, which efficiently binds small molecules [30.151]. Therefore, MUPs have initially been attributed a carrier function for small volatile ligands to facilitate their transmission to the VNO lumen and delay their release after environmental excretion [30.151]. Today, it has become increasingly clear that a *tailored* urinary MUP excretion of only 4–12 protein types per individual carries some identity information. Moreover, MUPs alone, without associated small molecules, stimulate basal V2R-positive VSNs [30.69, 79, 145], thereby promoting such different behaviors as male territorial aggression [30.69, 145], female conditioned place preference [30.152, 153], or, if emitted by heterospecifics, innate fear [30.79].

Somewhat similar to formylated peptides, MHC class I peptide ligands are another example of chemosensory signaling components with a prominent immune system function [30.154]. These relatively small peptides are detected by both V2R-positive basal VSNs as well as neurons in the MOE [30.60, 76, 155]. MHC peptides are part of the urinary *peptidome* [30.156] and, as such, they are stably secreted throughout life, providing a potential means for representation of individuality. Strikingly, MHC class I peptide ligands were the first and so far the only molecularly defined chemosignals shown to mediate selective pregnancy block (or *Bruce effect*), which is associated with the formation and maintenance of an olfactory recognition memory by the vomeronasal system [30.76, 157].

A total of 38 mouse genes encode ESPs [30.74]. These peptides are emitted in lacrimal, Harderian, and submaxillary gland secretions and differentially expressed between genders and across development [30.74, 142]. Two ESPs were studied in detail, ESP1 and ESP22. Both are found in male tear fluid and activate basal VSNs with high selectivity [30.142, 144]. While ESP1 expression is male-specific, expression of ESP22 is age-dependent. Both peptides induce robust, though very different behavioral responses in females and males, respectively: ESP1 stimulates lordosis, a receptive female mating posture [30.59], whereas ESP22 is a juvenile mouse pheromone that inhibits sexual behavior in adult male conspecifics [30.144].

Volatile urine-enriched gender-specific bioactive ligands were identified by means of gas chromatography-mass spectrometry. Among the described urinary constituents were several vomeronasal in vitro ligands such as 2-sec-butyl-4,5-dihydrothiazole, 3,4-dehydro-exo-brevicomin, 6-hydroxy-6-methyl-3-heptanone, α/β-farnesene, 2-heptanone, isoamylamine, and others [30.146, 158, 159]. Interestingly, these compounds bind MUPs [30.160], are able to directly activate VSNs at extraordinarily low concentrations [30.75], and promote behavioral responses such as puberty acceleration or delay in females [30.161, 162].

30.3 The Septal Organ

The septal organ of Masera and the Grüneberg ganglion (Sect. 30.4) are undoubtedly the most enigmatic olfactory subsystems in the mammalian nose. First described in detail in 1943 by the Italian anatomist *Rodolfo-Masera* [30.163], chemosensory research had neglected the *Organ of Masera* for a long time. Accordingly, few aspects of the SO physiology have been elucidated and various basic questions about the organ and its functional relevance remain unresolved.

In mice, the SO is a small, isolated patch of sensory neuroepithelium that, surrounded by respiratory epithelium, is bilaterally located near the base of the nasal septum close to the nasopalatine duct openings (Fig. 30.1). The SO epithelial organization closely resembles the structure of the MOE. However, the generally thinner neuroepithelium is composed of only up to three layers of ciliated bipolar OMP-expressing OSNs (compared to six to eight layers in most regions of the MOE) [30.3]. Entering the brain through a defined perforation of the cribriform plate, axons of SO neurons project exclusively to a small subset of glomeruli in the main olfactory bulb [30.1]. Approximately 30 glomeruli, clustered at the ventromedial aspect of the bulb, receive substantial synaptic input from the SO and a few of these glomeruli might actually be exclusively innervated by SO neurons [30.164].

Gene expression profiling in the SO provided evidence for a canonical signaling machinery expressed in SO neurons. While a very small subset of cells appear to express both GC-D and PDE2 (Sect. 30.5.2), the majority SO sensory neurons express canonical odorant receptors, $G_{\alpha olf}$ and adenylate cyclase III [30.165, 166]. Results from microarray analysis and large-scale reverse transcription polymerase chain reaction exper-

iments suggest that not the entire repertoire of ORs is present in SO neurons. Rather a distinct group of 50–80 OR genes, all class II receptors of various families, are expressed in both the MOE and SO [30.167, 168]. Interestingly, OR expression in the SO is not randomly distributed. While apparently abiding by the *one neuron – one receptor* rule, > 90% of SO neurons express one of only nine ORs [30.168]. SR1 (also known as *mOR256-3*) is by far the most abundant receptor found in ≈ 50% of all SO neurons. OSNs that express SR1 respond to many, structurally unrelated odorants over a wide concentration range, whereas OSNs expressing a gene-targeted SR1 locus that lacks the SR1 coding sequence do not show this broad responsiveness [30.169]. The *broad tuning profile* of this specific, most abundant SO receptor likely reflects early reports of broad general odor sensitivity of the SO [30.170].

What functional role is played by the SO? Its unique strategic location in the nasal cavity has prompted speculation about a function as an alert sensor during quiet respiration, when air flow does not reach the entire MOE [30.165]. Others have suggested that the SO may detect compounds of low volatility [30.24]. Whatever its exact role(s), the SO has evolved as a unique *outpost* of the olfactory system that is likely involved in a specific chemosensory function.

30.4 The Grüneberg Ganglion

In 1973, *Grüneberg* discovered an arrow-shaped *ganglion of unknown function* [30.171] at the anterior end of the nasal cavity [30.3]. It bilaterally lines the rostro-dorsal nasal septum close to the opening of the naris [30.172] (Fig. 30.1). Originally considered to constitute a part of the *Nervus terminalis*, the GG was ignored for decades. However, the lack of terminal nerve marker expression and more recent anatomical and functional evidence suggest that the GG represents an independent chemosensory subsystem. Since its *rediscovery* a few years back, the ganglion's peculiar anatomy and elusive physiology have sparked new interest within the field of chemosensory neuroscientists.

GG neurons express OMP and project axonal processes to glomeruli in defined olfactory bulb areas [30.172, 173]. However, GG neurons are devoid of cilia or microvilli that represent hallmarks of other chemosensory neurons in the nose. Moreover, light and scanning electron microscopy show that the GG lacks direct access to the nasal cavity [30.1, 174]. This has fueled speculation about a function as a detector of gaseous or other highly membrane permeant stimuli [30.1]. By contrast, studies have reported expression of several chemosensory receptors in GG cells, including V2Rs and TAARs [30.175, 176] as well as elements of a cyclic guanosine 3',5'-monophosphate (cGMP) pathway [30.177]. GG neurons project along the dorsal nasal septum and medial olfactory bulb surface to dorso-caudal regions near the AOB [30.172, 178] that somewhat overlap with the area occupied by the necklace glomeruli (see below).

A sensory function of the GG subsystem has been proposed on the basis of behavioral data [30.174] and later demonstrated by physiological recordings from GG cells [30.179–181] as well as immediate early gene activity assays [30.182, 183]. So far, however, different studies/approaches have yield rather controversial results. Thus, further physiological investigation is required to unify our concept of GG chemosignaling.

30.5 Noncanonical Olfactory Signaling Pathways in the Main Olfactory Epithelium

More than two decades ago, the discovery of the rodent OR gene family by *Linda B. Buck* and *Richard Axel* marked the beginning of the molecular era of chemosensory research [30.10]. As such, this landmark finding was a watershed event for understanding olfaction. Since 1991, however, a number of additional studies have greatly expanded the classes of receptor genes and proteins implicated in chemosensory signaling. Compared to major advances in understanding canonical olfactory signaling, our current concept(s) of chemodetection mechanisms, signaling pathways, and information coding principles in OR-independent olfaction are still in their infancy. We are only just beginning to unravel the secrets of noncanonical chemosignaling.

30.5.1 Trace Amine-Associated Receptor (TAAR)-Expressing Neurons

Given the vast dimensionality in *odor space* [30.184, 185], the growing appreciation for parallel processing of socially relevant odors by both the main and accessory olfactory system [30.13], as well as the

discovery of different chemoreceptor families in the VNO [30.38, 49–51], it was tempting to speculate that canonical ORs might not represent the only GPCR family serving as MOE chemosensory receptors. In 2006, *Liberles* and *Buck* identified expression of members of the trace amine-associated receptor (TAAR) family in OSN-enriched mouse cDNA samples [30.186]. Like ORs, TAARs appear to be monoallelically expressed in sparse, nonoverlapping subsets of mouse OSNs and localized both in cilia, the site of odor detection, and in axons, where they may serve a guidance function [30.186, 187]. Early on, these properties strongly suggested an olfactory role. Phylogenetically, *Taar* genes are related to other aminergic GPCRs such as metabotropic dopamine and serotonin receptors [30.188]. While $\approx 25\%$ of ORs are suspected pseudogenes [30.189], only one *Taar* gene, *Taar7c*, appears pseudogenized, suggesting that the burden of pseudogene selection is significantly lower in TAAR-expressing neurons [30.187]. Moreover, the *Taar* repertoire is evolutionarily retained in mammals and many intact *Taar* genes are also found across diverse vertebrate genomes, from zebrafish to humans [30.186, 190] further substantiating a common, rather than species-specific olfactory role that is not met by the much larger repertoire of canonical ORs.

Apparently, the expression of ORs and TAARs is mutually exclusive since fluorescence in-situ hybridization studies did not identify OSNs coexpressing both receptor types [30.186]. The regulatory logic of *Taar* expression, however, is different from OR gene choice. *Taar* genes lack the epigenetic signature of OR selection. Moreover, knockout of a specific *Taar* allele resulted in frequent expression of a second *Taar* without silencing the deleted allele [30.187]. These differences are further substantiated by recent findings indicating that TAAR neurons form a sensory neuron population restricted to *Taar* expression prior to initial receptor gene choice [30.191].

Both ORs and TAARs transduce chemostimuli through a signaling mechanism that employs G proteins and an increase in cAMP [30.1]. As initially predicted [30.188], mouse TAARs respond to biogenic amines such as isoamylamine, 2-phenylethylamine and trimethylamine (activating mTAAR3, mTAAR4, and mTAAR5 proteins, respectively). TAAR5 was shown to mediate a species-specific attraction response to trimethylamine. Interestingly, phylogenetic analysis of related rodents suggests that synchronized evolution of trimethylamine biosynthesis pathways and odor-evoked behavioral responses could ensure species-appropriate social interactions [30.192]. Further evidence for a selective function of olfactory TAARs as detectors of socially and/or behaviorally relevant odors has been provided by Ferrero and coworkers [30.193]. Heterologously expressed TAAR4 is activated by carnivore urine and the TAAR4 ligand 2-phenylethylamine enriched in urine samples from carnivore species. Furthermore, this predator-derived cue promotes innate avoidance behavior and increases stress hormone release [30.193]. The exquisite sensitivity of TAAR4 for 2-phenylethylamine gave rise to an alternate (though by no means mutually exclusive) interpretation – that this phylogenetically distinct class of aminergic receptors is simply required for high-sensitivity detection of amines: innately aversive odours [30.191].

The majority of TAAR neurons project to a discrete cluster of glomeruli in a confined bulb region between the previously characterized DI and DII domains in the dorsal olfactory bulb of the mouse [30.191]. In vivo glomerular imaging in this region confirmed that dorsal TAAR glomeruli are selectively activated by volatile amines at low concentrations and further revealed that aversive amines are represented in a nonredundant fashion [30.194].

Together, these recent findings all strongly suggest that TAAR neurons constitute a distinct olfactory subsystem with unique molecular and anatomical features. The TAAR subsystem may thus provide a hard-wired, genetically and anatomically distinct, parallel input stream in the main olfactory pathway that is specialized for the detection of volatile amines [30.191].

30.5.2 Receptor Guanylyl Cyclase-D (GC-D)-Expressing Neurons

The repertoire of olfactory receptors is not restricted to GPCRs. A small percentage of OSNs express neither ORs nor TAARs, but a type-D receptor guanylyl cyclase (GC-D) [30.195]. Receptor GCs are expressed in many tissues of numerous species. They include both orphan and peptide receptors [30.196]. Initially isolated from sea urchin sperm, receptor GCs serve diverse functions including marine invertebrate sperm chemotaxis, regulation of diuresis, transduction in mammalian photoreceptor cells as well as nematode chemosensation [30.196–198]. Receptor GCs share an evolutionary conserved structure: an extracellular receptor domain is coupled by a single transmembrane helix to an intracellular regulatory (kinase homology) and a catalytic domain [30.196, 197]. Ligand binding to the extracellular receptor domain – in mammals, these ligands are mostly natriuretic peptides [30.197] – triggers cyclase domain activity and, consequently, the elevation of intracellular cGMP.

For years, the functional role of GC-D in olfaction has remained mysterious. OSNs that express the GC-D protein also express a variety of putative signaling pro-

teins that could be involved in a cGMP-dependent transduction cascade, for example, the cGMP-gated cyclic nucleotide-dependent channel subunit CNGA3 or the cGMP-stimulated phosphodiesterase PDE2 [30.199, 200]. By contrast, GC-D$^+$ neurons lack many components of the canonical olfactory signaling pathway [30.198, 201]. The phylogenetic conservation of *Gucy2d*, the GC-D encoding gene, across many mammalian species suggests a common olfactory function. As for most vomeronasal receptors, however, humans and other primates are a notable exception.

Do GC-D neurons respond to *conventional* odors or other chemostimuli? And, if so, is GC-D itself the cellular receptor? Studies in gene-targeted mice and heterologous expression systems strongly suggest that GC-D neurons are critical for the detection of natriuretic peptides and/or gaseous stimuli [30.202–205]. As regulators of fluid balance in the kidney and intestine, uroguanylin and guanylin activate enterocytes via guanylyl cyclase C (GC-C), which leads to cGMP-dependent inhibition of Na^+/H^+ exchange and activation of the cystic fibrosis transmembrane regulator [30.206]. Both peptide hormones induce responses in the MOE, even in recordings from *Cnga2* null mice (which are often referred to as *anosmic* as these animals lack a CNG channel subunit essential for canonical OSN signaling). This peptide-induced activity, however, is completely abolished when mice lack either *Gucy2d* or *Cnga3*, the gene encoding the cGMP-dependent CNG channel subunit [30.204]. Single cell recordings from identified GC-D neurons confirmed their sensitivity to uroguanylin and guanylin as well as to diluted urine samples. Strikingly, GC-D neurons showed exquisite peptide sensitivity with half-maximal neural activity stimulated by peptide concentrations as low as 66 pM.

Small gaseous molecules have also been shown to stimulate GC-D neurons. Initially, the small population of *Gucy2d*-expressing olfactory neurons was proposed to function as a CO_2 sensor [30.203]. Coexpression of GC-D and carbonic anhydrase type II indicates that enzymatic catalysis of CO_2 by carbonic anhydrase might characterize this noncanonical olfactory signaling pathway. A few years later, another gaseous molecule, carbon disulfide (CS_2), was found to stimulate GC-D$^+$ OSNs. Using gene-targeted mice, *Munger* and coworkers showed that both chemosensory responses to CS_2 and CS_2-dependent socially transmitted food preferences are drastically reduced in mice lacking GC-D, CNGA3, or carbonic anhydrase type II [30.205]. Their findings indicate that GC-D$^+$ OSNs detect chemosignals that facilitate food-related social interactions via associative olfactory learning.

GC-D neurons not only display unique signaling protein expression, but are also distinct in their glomerular projection pattern. Necklace glomeruli, a peculiar and still poorly defined chain-like band of glomeruli that run between the main and the accessory bulb, are the sole olfactory bulb targets of GC-D$^+$ OSNs [30.207–209]. In contrast to the apparently homogeneous innervation of glomeruli from canonical OSNs, each necklace glomerulus receives heterogeneous innervation from at least two sensory neuron populations: GC-D neurons and an OMP$^+$/GC-D$^-$ neuron population [30.207]. This disparate functional topology underscores the notion that very different coding principles describe both subsystems.

30.6 Olfactory Subsystems in Humans?

Do functional olfactory subsystems exist in humans? Especially the role of a human VNO, with respect to a potential biological significance of proposed human pheromones, has been controversially discussed both within the field as well as in a more popular scientific context. So far, not a single human pheromone has been chemically identified [30.137, 139]. Among the many reasons for that are the inherent difficulties to identify robust and reproducible effects when working with human subjects [30.210]. As recently pointed out by Peter Brennan, this does not necessarily mean that human pheromones do not exist, but complexities of modern human society may diminish their biological significance and make it difficult to identify consistent effects [30.211]. So, may human pheromones yet be found in the future? Candidate sources of such chemosignals are axillary sweat, areolar secretion of lactating women, and tear fluid [30.212–214]. The existence of human pheromones as constituents of such complex bodily secretions is, for instance, suggested by odor-mediated menstrual synchrony in female roommates which was observed in some studies, but not in others [30.4]. Whatever the molecular nature and physiological function of any such behaviorally relevant chemical, designation as a *pheromone* might be particularly problematic in humans. Probably, as has been proposed by Wyatt, the term *signature odor(s)* might be a more useful classification [30.138, 139].

If human signature odors exist, they are not detected and processed by an accessory olfactory system. While an embryonic structure that somewhat resembles a VNO is present early in human fetal devel-

opment, anatomical evidence shows that any residual structure that has been proposed as the adult human VNO – the *vomeronasal pit* – is clearly nonfunctional [30.215–217]. The vomeronasal pit is an epithelial diverticulum in the adult human nasal septum that does not have a similar structure or function to the rodent VNO [30.157]. Cells in the pit do not express OMP [30.218], the signature protein of mature olfactory/vomeronasal neurons in other mammals [30.219]. Moreover, while vomeronasal nerves appear to play a vital role during human fetal development in guiding LHRH neuron migration to the hypothalamus [30.157], no axonal connections to higher brain centers remain in the adult [30.215, 216]. These anatomical findings are corroborated by an overwhelming amount of molecular evidence. Almost all genes encoding for rodent vomeronasal receptors and VNO-specific transduction proteins are pseudogenes in humans. All but five *V1r* orthologs [30.220], all *V2r*s, vomeronasal *Fpr*s, and *H2-Mv* genes, as well as *TrpC2* [30.221] are nonfunctional in the genomes of both humans and Old World monkeys. The relaxation of selective pressure on the *TrpC2* gene, and probably other VNO-specific genes, occurred approximately 23 million years ago, coincident with the acquisition of trichromatic color vision in the common ancestor of Old World monkeys and apes [30.222]. Moreover, gene families that encode important vomeronasal peptide/protein stimuli in rodents, such as MUPs and ESPs, are also absent from the human genome.

More evidence for the lack of an accessory olfactory system in humans comes from anatomical studies in the central nervous system. While an AOB of different size and degree of differentiation is found in most adult nonaquatic mammals, this structure is absent in Old World monkeys, apes, and humans [30.223]. Quite similar to the transient embryonic development of a fetal VNO, a well-developed fetal AOB that regresses in later stages of development has been reported in humans and apes [30.32].

While we know little about human signature odors and remnants of a VNO, hardly any evidence is currently available for (or against) the existence of other olfactory subsystems in humans. Although Grüneberg reported in his original publication that a Grüneberg ganglion is found in human embryos [30.171], the organ likely regresses during fetal development [30.210]. Likewise, a human septal organ has not been found. For noncanonical subpopulations of OSNs, it is clear that at least five members of the *Taar* gene family are potentially functional in humans [30.4]. Whether TAARs are expressed in neurons of the human olfactory epithelium, however, is not clear. For the other main class of noncanonical OSNs, the GC-D neurons, it has been shown that GC-D is also pseudogenized in primates, and, in addition, human necklace glomeruli have not been described [30.210].

30.7 Glossary

- *Accessory olfactory bulb (AOB)*: Structure of the olfactory forebrain in the dorsal posterior region of the olfactory bulb. All VSN axons terminate in the AOB where they form synapses with second-order mitral cells.
- *Action potential*: Short-term change in membrane potential in response to stimulation; also known as *nerve impulse* or *spike*; a neuron that emits an action potential (or *trains* of action potentials) is often said to *fire*.
- *Amygdala*: Structure in the forebrain that is an important component of the limbic system and plays a central role in emotional learning.
- *Anoctamins*: The anoctamin (TMEM16) family of membrane proteins are, at least in part, Ca^{2+}-activated Cl^{-} channels; the term *anoctamin* was coined as these channels are anion selective and have eight transmembrane segments.
- *Broad/Narrow tuning profile*: The sensitivity range of a sensory neuron that significantly changes its action potential discharge in response to either a wide range of different stimuli (broad tuning) or a very precise subset of stimuli (narrow tuning).
- *Bruce effect*: Termination of pregnancy by chemosensory cues (pregnancy block); occurs when a recently impregnated mouse aborts her litter in response to chemosensory cues from an unfamiliar male.
- *Chemotopy*: Physical distribution of neurons/glomeruli on the surface of the olfactory bulb with respect to their individual receptive fields for odorants.
- *Cribriform plate*: A sieve-like structure between the anterior cranial fossa and the nasal cavity; part of ethmoid bone that supports the olfactory bulb; perforated by foramina for the passage of olfactory nerve fibers.
- *Dendrodendritic synapses (in MOB/AOB)*: Reciprocal synapses between two dendrites (here, from a mitral and granule cell); in contrast to axodendritic

synapses that are polarized from an axonal bouton onto a dendrite.

- *Deorphanization*: The process, which results in the identification of a natural ligand acting on an orphan receptor.
- *Diencephalon (Diencephalic, adj.)*: Posterior part of the forebrain that connects midbrain with cerebral hemispheres; encloses the third ventricle, and contains the thalamus and hypothalamus, and associated areas.
- *G Protein-coupled receptor (GPCR)*: Large superfamily of receptors with a characteristic seven-transmembrane topology; binding of extracellular ligands (or activation by light in cases of *opsins*) activates heterotrimeric intracellular G protein signaling cascades; typical GPCRs are receptors for hormones, neurotransmitters, visual, and chemosensory (olfaction and taste) stimuli.
- *Ganglion*: A nerve cell cluster or a group of nerve cell bodies located in the peripheral nervous system.
- *Gene cluster*: Groups (clusters) of two to several dozens of genes belonging to the same gene family; the vast majority of OR, V1R, and V2R genes in mice are found in clusters scattered throughout the genome.
- *Glomerulus (Glomeruli, pl)*: Specific structure/functional unit of spherical neuropil in the outer layers of both the main and accessory olfactory bulb; glomeruli consist of synapses of OSN/VSN axons with apical dendrites of mitral, tufted, and periglomerular cells; they segregate and organize synaptic inputs and, thus, form an olfactory topographic map (*chemotopy*) that allows the interpretation of transmitted chemical signals to the brain.
- *Heterologous expression*: Expression of a gene (or part of a gene) in a host cell or organism, which does not endogenously express this gene or gene fragment.
- *Hypothalamus*: Complex brain structure composed of many nuclei with various functions; regulator of internal organ activities by monitoring information from the autonomic nervous system, controlling the pituitary gland, and regulating sleep and appetite.
- *Input resistance*: The input resistance of a neuron reflects the extent to which membrane channels are open; it is defined as the change in voltage associated with injection of a current (divided by the input current); an increase in input resistance means a greater change in membrane potential in response to a current, thus rendering a neuron more excitable.
- *Interneurons (in MOB/AOB)*: Periglomerular and granule cells, inhibitory neurons of both the main and accessory olfactory bulb; both function to inhibit mitral cells via feed-forward and feedback reciprocal dendrodendritic synapses.
- *Kairomones*: Chemosignals transmitted between species (interspecific chemical cues) that benefit a member of another species without benefitting the emitter. For example, the presence of a predator might be signaled by kairomones.
- *Major histocompatibility complex (MHC)*: Group of genes that code for cell surface proteins that *present* both endogenous and exogenous protein fragments to cells of the immune system; recognition of foreign substances triggers an immune response; MHC proteins are found in all higher vertebrates; the human MHC is frequently referred to as the human leukocyte antigen (HLA) system.
- *Monoallelic expression*: By default, both alleles of a gene are actively transcribed (biallelic expression); in few cases, however, a single allele of a given gene is expressed (X-linked genes in females as a result of X chromosome inactivation).
- *Monogenic expression*: Exclusive expression of a single gene (or pair of allelic genes) from a family of related genes.
- *Olfactory placode*: Thickening of ectoderm that arise through cell division during neural tube formation; the olfactory system is one peripheral nervous system component that arises from paired sensory placodes during development; olfactory placodes give rise to OSNs, supporting and basal cells of the olfactory epithelium [30.224].
- *Ontogeny*: Origin and development of an individual organism from embryo to adult.
- *Orphan receptors*: Receptors for which no ligand is known.
- *Pheromones*: Molecules used for conspecific chemical communication (intraspecific chemical cues). Originally defined by Karlson and Lüscher as chemicals that are released by one member of a species causing specific reactions in other members of the same species [30.136].
- *Plexiform layer*: Meticular layer (of the retina or the olfactory bulb) mostly consisting of nerve cell processes (neuropil) and situated between layers of cell bodies.
- *Projection neuron*: Mitral cell in the MOB and AOB (and/or tufted cell in the case of the main olfactory bulb); these neurons receive information from OSNs or VSNs and relay or *project* this information to higher order brain nuclei.
- *Telencephalon (telencephalic, adj.)*: Anterior part of the forebrain that constitutes the cerebral hemispheres and related structures.

- *Tetrodotoxin (TTX)*: A potent neurotoxin found in pufferfish; inhibits action potential firing by binding to and blocking voltage-gated sodium channels.
- *Transient receptor potential (TRP) channels*: Ion channels named after the role of the channels in *Drosophila* phototransduction; mammalian *Trp* genes are encoded by at least 28 channel subunit genes; channels form six protein families; primary structures predict six transmembrane domains with a pore domain between the fifth and sixth segments and both C and N termini presumably located intracellularly [30.225].
- *Vomeronasal sensory neurons (VSNs)*: Bipolar sensory neurons that reside in the sensory epithelium in the VNO. VSN dendrites end in microvilli, which represent the site of chemosensory transduction. Accordingly, all relevant transduction molecules, such as V1/2R and FPR receptors as well as the transient receptor potential channel 2 (TRPC2) are located in the microvilli. The axons of VSNs terminate at glomeruli in the AOB, where they form synapses with second-order projection neurons (mitral cells).

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