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The olfactory bulb and central pathways

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Key words. Odor biology; olfactory bulb; piriform cortex; mitral cells; tufted cells; mediodorsal thalamus; olfactory tubercle.

This review of central olfactory system structure and function will concentrate on pathways involving the vertebrate main olfactory bulb. Other species and issues, including the vomeronasal system, are discussed in other reviews of this series.

The olfactory periphery

There is a rapidly expanding literature on the olfactory receptors and receptor processes that is outside the scope of this review. However, it is important to note the spatial localization of odor responses and the spatial organization of projections from the epithelium to the olfactory bulb.

Odor sensitivity is differentially localized on the receptor sheet. This localization is determined by the position of the receptor cell relative to the air flow[78] and by intrinsic properties of the receptor cell[42, 62, 76, 83]. The olfactory epithelium projects topographically to the olfactory bulb[10, 15, 20, 50, 63] maintaining the spatial localization of the peripheral odor response in the first stage of central projection. A crude spatial segregation of odor responsiveness has also been demonstrated with 2-deoxyglucose in the olfactory bulb of rats[9, 40, 128] and tree shrews[123].

The olfactory bulb

The olfactory bulb is a laminated structure with a generally ellipsoid form in the mammal. The figure illustrates the layers as described in the rat and hamster. Certain differences exist in other species. This description of the layers follows that by Shepherd[119, 120] and many details not mentioned here can be found in his reviews. The four major cell types of the bulb will be introduced first and their details developed in the description of the layers.

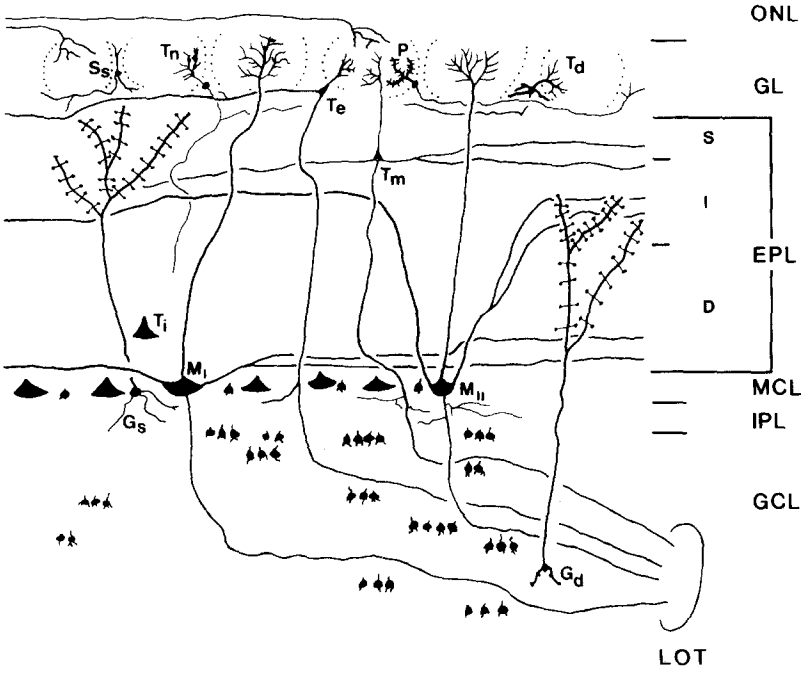
The term mitral/tufted cell refers to a general class of neurons with smooth apical dendrites receiving synapses from the olfactory nerves in the glomeruli. The mitral cells are the largest and all lie in a single layer called the mitral cell body layer (MCL). The several classes of tufted cells lie superficial to the MCL. Granule cells are small axonless interneurons with somata deep to the MCL and dendrites crossing several layers. Periglomerular cells are small neurons with dendrites that also enter the glomeruli. A variety of other interneurons, collectively referred to as short axon cells, can be seen in various layers of the bulb.

Olfactory nerve and glomerular layer

The olfactory nerve layer (ONL) contains the fine unmyelinated axons of receptor cells that terminate on mitral/tufted dendrites in the underlying glomerular layer. The glomerular layer (GL) consists of the glomeruli and the surrounding periglomerular region. The spherical glomeruli contain no neuronal somata but are penetrated by primary nerves, by the smooth apical dendrites of mitral/tufted cells, and by the spiny dendrites of periglomerular cells[89,90].

The periglomerular region contains somata of periglomerular cells, superficial short axon cells, and a type of tufted cell with no basal dendrites[89,107]. The spiny intraglomerular dendrites of periglomerular cells enter into reciprocal dendodendritic synapses with mitral/tufted dendrites[89,90] and in some animals the periglomerular cell also receives olfactory nerve synapses[90,135,136]. The axon of the periglomerular cell leads away from the region of the principal dendrite and distributes in the periglomerular region[89,107]. Many of the periglomerular cells contain the enzyme pathway for producing GABA (glutamic acid decarboxylase) and many contain the pathway for producing dopamine[34,35]. A recent report[79] indicates that these transmitters are found in different populations of periglomerular cells.

The physiology of periglomerular cells is not clearly worked out. Some cells of the glomerular layer are suppressed by nerve stimulation when that stimulation is successful in producing a response from the cell[27,118]. This result was interpreted, in the light of dendrodendritic synapses between mitral/tufted cells and periglomerular cells, as indicating that periglomerular cells inhibit the presynaptic mitral cells thus turning off their input. On the other hand, summed post-stimulus-time histograms of cells in the periglomerular regions do not show the oscillatory behavior expected of cells in a strong negative feedback loop[19]. Current source density analysis suggests a depolarization of vertically oriented processes spanning the EPL that would correspond in time to excitatory periglomerular input to mitral cells[66]. None of these reports identified the particular cells involved. Activation of the olfactory bulb through the olfactory nerve produces a longer lasting suppression of mitral cell activity than does activation by the antidromic route[21], suggesting a mechanism of suppression at the glomerular level.



Drawing of the layers of the olfactory bulb based on data from rat and hamster. Within the glomerular layer (GL), the glomeruli, represented by dotted lines, receive axons from the olfactory nerve layer (ONL). The periglomerular region, surrounding the glomeruli, contains somata of periglomerular cells (P), superficial short axon cells (Ss) and some tufted cells (Tn = tufted cells with no basal dendrites; Td = tufted cells with densely branching dendrites). The external plexiform layer (EPL) can be divided into three zones: superficial (S), intermediate (I) and deep (D). Within these zones lie the somata of tufted cells with long, sparsely branching dendrites (Te = external tufted cell, Tm = middle tufted cell, Ti = internal tufted cell). The mitral cell layer (MCL) contains cells with two extremes of dendritic morphology (MI and MII) and some granule cells. The internal plexiform layer (IPL) contains collaterals of mitral and tufted cells. The granule cell layer (GCL) contains two extremes of granule cells: superficial cells (Gs) with spines in the intermediate and superficial zones of the EPL and deep cells (Gd) with spines in the intermediate and deep EPL. Axons from many mitral and tufted cells pass through the GCL toward the lateral olfactory tract (LOT).

The superficial short axon cell is larger than the periglomerular cell. Its soma and dendrites are found in the periglomerular region (i.e. outside the glomeruli) and upper external plexiform layer[89, 107]. The axons of these cells ramify primarily in the periglomerular region but can occasionally be traced across the EPL into the granule cell layer[91, 107]. Immunohistochemistry suggests that superficial short axon cells contain glutamic acid decarboxylase[34, 80] and may therefore be inhibitory.

External plexiform layer (EPL)

The EPL lies between the GL and the mitral cell layer (MCL). In the rat, it has been useful to divide the EPL into three sublaminae or zones: superficial, intermediate and deep. In cytochrome oxidase stained material, the intermediate zone has a darker appearance than the superficial and deep zones[77]. The intermediate zone contains a larger number of tufted cell somata than the deep zone. Macrides and Schneider[61] found it useful to describe a glomerular border region of the EPL which lies in the scalloped infoldings between the bottom of glomeruli. The major cell type of the EPL is the tufted cell, all of which have at least one smooth apical dendrite entering a glomerulus. Historically, the tufted cells have been subcategorized by the positions of their somata into three types: external, middle and internal[101]. More recently, other distinctions have been described and this discussion will reflect these new results. The tufted cell without basal dendrites has been mentioned. Its soma lies in the periglomerular regions or in the glomerular border region of the EPL. A tufted cell with short densely branching dendrites is found primarily in the glomerular border region and superficial zone of the EPL[61]. Immunohistochemical staining shows that many tufted cells in the glomerular border region of the EPL contain substance P[8, 12], though the exact morphological type and projections of these cells is not yet clear.

Other tufted cells have longer, sparsely branching basal dendrites, similar in form but shorter than those of mitral cells. These dendrites have dendrodendritic synaptic contacts with granule cells[90]. In the superficial zone of the EPL, the external tufted cells with sparsely branching basal dendrites cells usually have ovoid cell bodies and strongly asymmetric basal dendritic fields[61, 88]. The middle tufted cells in the intermediate zone of the EPL have more triangular cell bodies and longer, symmetrically radiating dendrites[61, 88]. The internal tufted cells also have sparsely branching basal dendrites. These cells have not been extensively described in the rodent, but in the rabbit[45, 69] internal tufted cells (or displaced mitral cells) have basal dendrites that pass superficially to mingle with those of middle tufted cells.

Retrograde transport studies have shown that some tufted cells project an axon into the lateral olfactory tract[30, 124] while others are probably interneurons[109]. The external tufted cell axons project only short distances while the deeper cells project more caudally[30, 109, 113, 124]. Few, if any, middle or external tufted cells project to the posterior part of the piriform cortex. The morphological subtypes described above have been difficult to evaluate in retrograde transport studies because the dendrites have not been well filled and cells have been identified by the positions of their somata. Intracellular or extracellular injections of horseradish peroxidase have been used to study the axons of cells[45, 88] but this has been most successful with larger cells that have long dendrites. External and middle tufted cells with long, sparsely branching basal dendrites both have axons that leave the bulb. The axons of these cells pass directly across the EPL without collaterals in the vicinity of the glomeruli or in the EPL but they give off extensive collaterals in the internal plexiform layer[45, 88]. The internal tufted cells (or displaced mitral cells) studied in the rabbit[69] show a similar axon collateral pattern.

These data on dendritic morphology and immunocytochemistry suggest that redefinition of these cell types may be in order. Subpopulations of tufted cells have been stained with several of the immunohistochemical procedures for putative synaptic transmitters and modulators without staining of mitral cells[58]. Cholecystokinen-like immunoreactivity[116], on the other hand, is more prominent in middle tufted cells, though it is not exclusively present there. It may turn out that these substances will be as important as morphology in defining tufted cell function. On the other hand, this staining may change with stimulation or developmental conditions. An example is modulation of tyrosine hydroxylase staining by deafferentation[2].

Mitral cell layer

The mitral cell layer (MCL) consists of a single thickness of mitral cells and occasional interspersed granule cells. The mitral cells are the largest of the bulb, with diameters averaging around 22 × 15 μm in the rat and hamster[61, 88]. Rat and hamster mitral cells have a single apical dendrite extending into a glomerulus and about 3–7 basal dendrites lying in the EPL. These long basal dendrites (with lengths ranging up to about 900 μm in the rat) receive the granule cell dendrodendritic synapses. In the rat, there are at least two forms of mitral cells as judged by their basal dendrites and axon collaterals[88]. Type I mitral cell basal dendrites are confined to the deep zone of the EPL. Type II mitral cells have fewer basal dendrites with fewer branches, and those branches ramify primarily in the intermediate zone of the EPL. Unlike Type I mitral cell axons, Type II mitral cell axons frequently branch close to the cell body. The rabbit and rat appear to differ in mitral cell morphology, since the rabbit mitral cells with superficial dendrites have somata displaced from the MCL like classic internal tufted cells.

Internal plexiform layer

The internal plexiform layer (IPL) is a thin region between the MCL and the first large grouping of granule cell somata. It contains few somata and is traversed by granule cell dendrites and mitral/tufted axons. Mitral/tufted axon collaterals ramify extensively in the IPL and it is likely that these collaterals contact granule cells or other interneurons since they cannot be traced back into the EPL[45, 88]. The collaterals may act on some interneuron

population to produce the synaptic activation of mitral and tufted cells reported[81] after electrical stimulation of the LOT.

Granule cell layer

The granule cell layer (GRL) contains somata of most of the granule cells, one of the major classes of inhibitory interneurons in the olfactory bulb. The small granule cells (8–10 μm in diameter) are the most numerous cell type in the bulb. They have no axons but have deep dendrites extending toward the center of the bulb and distal dendrites extending into the EPL. The distal dendrites extend laterally up to 250 μm. This distance is small relative to the diameter of the basal dendritic field of the mitral and many tufted cells. Spines or gemmules on the distal dendrites form reciprocal synapses[38,96] with the basal dendrites of mitral/tufted cells in the EPL. Shepherd has reviewed the evidence establishing the dendrodendritic interaction of granule cells with mitral/tufted cells[119,120]. At this reciprocal synapse, mitral/tufted dendrites release a transmitter that leads to depolarization of the granule cell. The granule cell then releases an inhibitory transmitter that hyperpolarizes the granule cell. Intracellular experiments[73] with paired pulse stimulation of the lateral olfactory tract (LOT) have supported the concept of dendrodendritic activation of the granule cells and have demonstrated that granule cells can produce action potentials[68]. The reciprocal synapse can also be effective without granule cell spikes during intracellular stimulation of turtle mitral cells[39] after action potential blockade with tetrodatoxin. Pharmacological[55,70,82] and immunohistochemical evidence[80,103] indicates that gamma-aminobutyric acid is the transmitter at the granule to mitral/tufted cell synapse.

Subpopulations of granule cells differ in their dendritic distribution within the EPL[69,87,134]. In the rat, the distal dendrites of the deepest granule cells reach only the deep zone of the EPL. The distal dendrites of the most superficial granule cells reach across the entire EPL but have spines only in the intermediate and superficial zones of the EPL. Since the spines are the site of dendrodendritic synapses with the mitral/tufted cells[38,96], it seems likely that these granule cell subpopulations differentially influence the mitral/tufted cell basal dendrites in these zones of the EPL. Other studies suggest that these granule cells differ neurochemically. The deeper granule cells of the rat show more enkephalin-like immunoreactivity[5] while more superficial granule cells show greater staining for glutamic acid decarboxylase (GAD)[80].

Species differences

Differences between the dendritic and axon collateral patterns between the rat and rabbit are noted above. The mitral cells can have multiple apical dendrites in the turtle[70] and rabbit[69] unlike the rat or hamster. The distribution of enkephalin-like immunoreactivity reported for the hamster GRL[12] is different from that of the rat. Switzer[131] has reported a variety of patterns of cellular lamination in the MCL and EPL across species. Such species variation is not surprising since similar variation is seen in other systems, as in the content of putative neurotransmitters in the layers of retina[6], for example.

Physiology of output cells

Single unit recordings show that not all output cells respond alike to afferent stimulation. The firing patterns of cells responding to clear air stimuli depend upon the position of the cell within the EPL[86]. Cells identified as mitral cells by being recorded at the MCL and antidromically activated from the LOT[27,117] respond with only single spikes to single pulse stimulation of the olfactory nerve, while more superficially located cells may respond with multiple spikes. Tufted cells identified by being antidromically activated from the LOT or olfactory tubercle, but not the posterior piriform cortex, are more easily excited by olfactory nerve stimulation than are mitral cells[108]. Tufted cells have lower thresholds, shorter latencies, give more multiple spikes to the nerve pulse stimuli, and (unlike mitral cells) rarely fail to respond.

Several authors[37,56,119] have speculated that the mitral/tufted to granule cell reciprocal synapse can mediate lateral inhibition as well as self-inhibition of mitral or tufted cells, and that lateral inhibition is important in the olfactory coding process. The observation of granule cell spikes[68] supports this speculation. The reciprocal synapses are activated during odor stimulation and are responsible for the induced wave responses to odor stimulation[22,112]. There is evidence that the local circuits in the bulb do shape the response to odors. Data from the salamander show that bulb cells[42–44] have more complicated patterns of response to odor than receptor cells[3,25]. These patterns include periods of excitation that outlast the stimulus and complex alternation of excitation and inhibition. Similar complex patterns have been seen in cells of the rat olfactory bulb[64,65]. The possibility that the local circuits of the bulb act to detect spatial contrast in sensory inputs has been tested only in the salamander[43] where punctate odor stimuli were presented to the epithelium during single cell recording from the olfactory bulb. Those units showed points of maximum response, and the response sign could change with different odors, but no direct evidence of contrast or antagonistic center-surround organization was seen. Until further tests are done, lateral inhibitory or surround antagonism models sensitive to the spatial distribution of input remain attractive. Such interactions may explain the complex patterns of odor response and the non-monotonic response of bulb cells to rising odor concentrations[42,64]. Resolution of the participation of the intrabulbar inhibitory circuitry in the pattern of odor responses is complicated by the complex form of the epithelium in mammals and by lack of detailed anatomical information on the amphibian olfactory bulb. Further progress will require control over stimulus position, odor concentration and the cell types being observed.

The direct terminal regions of the LOT

Mitral and tufted cell axons form the lateral olfactory tract (LOT) on the posterior lateral face of the olfactory bulb. The LOT is organized according to the origin of its

axons within the olfactory bulb. Dorsomedial, lateral and ventromedial regions of the bulb project respectively into dorsal, intermediate and ventral parts of the LOT[99, 109, 121]. Axon collaterals may branch from axons at any point within the cross sectional area of the LOT[113] and pass over the surface of the terminal regions forming a fiber layer (layer Iα)[31, 95]. These axons contact the dendrites of pyramidal and other cell types of the terminal regions in a superficial terminal region (layer IA). The thickness of layer IA grades from its thickest in rostral regions near the LOT, to thinnest in caudal regions distant from the LOT[110]. Most terminal regions also have a pyramidal cell layer (layer II) and a deep layer (layer III). Layers II and III contain cells that, in many regions, give off association axons to other parts of the terminal region[31, 32, 53] where they terminate primarily in layer IB and deeper layers[54, 95].

The anterior olfactory nucleus (AON) is the most rostral terminal region and, in some ways, one of the most complicated. It consists of five major subnuclei: the pars externa, pars dorsalis, pars ventralis, pars medialis and pars ventroposterior[32]. The AON is, in fact, cortical rather than nuclear in its structure, containing cells with basal and apical dendrites that receive their LOT inputs via layer IA and have other layered inputs. Many axons, but not all[84, 114], emit collaterals as the LOT crosses the pars externa of the AON. Some of these innervate the AON, while other longer collaterals pass to nearby piriform cortex and other structures. The projections from the bulb to the pars externa are topographically organized at this point[109, 115]. Some of these terminal branches arise from tufted cells, but many are collaterals of mitral cell axons projecting to more caudal centers[84, 115]. Within olfactory peduncle, the dorsal peduncular cortex and the tenia tecta also receive prominent direct olfactory projections[13, 95].

The olfactory tubercle is distinguished by the intrusion of the granule cell islands of Calleja across the superficial layers (see Fallon et al.[18] for a recent description). The tubercle receives inputs from mitral cells as well as tufted cells[30, 84, 108, 113, 114, 124]. A number of studies have indicated that the medial, posterior portion of the tubercle receives a greater input from ventral olfactory bulb than from the dorsal bulb[7, 67, 95, 97, 113]. The tubercle does not have significant association connections to other LOT terminal regions or centrifugal connections to the olfactory bulb[31]. Recent publications have emphasized that the putative transmitter content and other staining characteristics of the deep regions of the tubercle have much in common with the nearby regions of the striatum[18, 36].

The piriform cortex has a thinner pyramidal cell layer (layer II) than the AON. It is bounded by the AON rostrally, the olfactory tubercle and amygdala medially, the neocortex laterally, and the entorhinal cortex caudally. The endopiriform nucleus underlies much of the piriform cortex and receives some of its output[31]. Price and colleagues[31, 48] divided the piriform cortex into anterior and posterior parts based on the appearance of layer III. This separation is roughly at the posterior border of the olfactory tubercle. As noted above, the posterior piriform cortex receives only mitral cell axons from the bulb. Axons innervating the posterior piriform cortex pass in long, curved, nearly parallel paths. Golgi observations on the piriform cortex[127] show that some LOT axons give off short terminal branches along long stretches of their extent on the cortex, but it is not known whether an axon contacts cells of the cortex along its whole extent.

In at least some species, axons from the LOT reach across the piriform cortex to innervate a cortical region of different cytoarchitecture that lies along the rhinal sulcus. DeOlmos et al.[14] noted the fact that this region does not project axons into the olfactory bulb and referred to it as a transitional cortex. Recent workers in the mouse[122] have concluded that this region is ventral agranular insular neocortex. They reported electron microscopic evidence for bulbar axon synapses in this cortical region. Our unpublished observations from orthograde transport after injections of horseradish peroxidase into the olfactory bulb support this connection and its interpretation as agranular insular cortex. This transition region has the cytoarchitectonic structure of the rat ventral insular cortex[49]. Several publications recognize extension of the ventral agranular insular cortex below the rhinal sulcus[48, 53]. Projection of the olfactory bulb to insular cortex was first noted in the opossum where degeneration from olfactory bulb lesions was seen to cross the rhinal sulcus[67, 106]. This projection across the rhinal sulcus does not occur in our material from the rat, nor is it seen in the mouse[122] or hamster[13].

The entorhinal cortex is the most distant of the direct projections of the olfactory bulb[46, 104] and has the thinnest terminal layer[110]. The axons reaching the entorhinal cortex are from mitral cells, since all horseradish peroxidase injections into posterior LOT or piriform cortex label only mitral cells[113]. No recordings have been reported to test for odor responses in entorhinal cortex, but it has been shown that LOT axons directly contact pyramidal cells of the entorhinal cortex[104].

Spatial distribution of bulb output

Many investigators have commented on the diffuseness of the olfactory bulb projections. No sector of the bulb projects only to one local sector of the piriform cortex[7, 30, 67, 97, 99, 110, 113, 124]. Many mitral cells have collaterals innervating several regions of the piriform cortex and olfactory tubercle[52, 111]. Retrograde transport experiments show that this distributions of projection is not uniform or random[113]. Reconstructions of individually labeled neurons[84] show that the pattern of axon branching differs for individual cells. For example, many mitral cells had axon collaterals that innervated the olfactory tubercle and piriform cortex, while others innervated the piriform cortex alone. This is also supported in our electrophysiological[108, 111] and morphological[114] work. It is yet to be determined whether cells with different branching patterns have different responses to odor.

Association connections in primary terminal regions

The association connections within the piriform cortex have been studied physiologically as well as morphologically. Stimulation of the LOT produces two periods of

cortical excitation[28, 29, 33, 105]. Strong inhibitory interactions have also been observed in the piriform cortex[28, 29, 105]. There is a general topographic pattern of association connections within the central olfactory projection regions, such that regions distant from the LOT are strongly interconnected[31, 53]. Haberly and Bower[29] have demonstrated that the association axons arise, at least in part, from cortical pyramidal cells and have suggested that the association connections can also mediate inhibitory influences on cells of distant parts of the cortex. Most of the subnuclei of the AON participate in these associational projections[32, 53, 54], where their terminations are generally in layer IB or in deeper parts of the cortex.

Connections to thalamus and frontal cortex

The olfactory projections to thalamus and neocortex have received considerable recent attention. There are apparently three routes of olfactory projection to frontal neocortex: direct bulbocortical, corticortical and transthalamic connections. Direct bulbar projections to ventral agranular insular cortex have been discussed earlier in this review. Lateral regions of piriform cortex and entorhinal cortex project to agranular insular cortex[24, 53, 75, 102, 137]. The cortico-cortical connections to lateral orbital and ventral lateral orbital areas have been less extensively studied, but abstracts have described direct projections to the lateral orbital area from the anterior medial piriform cortex in the cat and rat[100, 137], and also report that the three cortical areas are interconnected.

The third olfactory route to the neocortex is through the thalamus. Olfactory inputs to the central segment of the mediodorsal nucleus of the thalamus are well established[4, 93, 98]. These projections rise from the cells of the deep layers of the olfactory tubercle (polymorph zone), and from the endopiriform nucleus deep to piriform cortex. The mediodorsal nucleus is reciprocally connected with the lateral orbital and ventral agranular insular cortices[47, 51, 98]. The olfactory tubercle and endopiriform nucleus of the adjoining medial piriform cortex project to the submedian nucleus of the thalamus[93, 98], which is reciprocally connected with a more medial region of frontal cortex, the ventral lateral orbital cortex[98].

Two regions of the monkey frontal cortex respond to electrical stimulation of the olfactory bulb and to odor stimulation[132, 139]. One region is the centroposterior orbital frontal cortex (CPOF), which was found to receive inputs through the mediodorsal thalamus. The second region is the lateroposterior orbital frontal cortex (LPOF), which does not appear to receive thalamic afferents. Potter and Nauta[92] found afferents to LPOF from the prorhinal cortex, a lateral extension of entorhinal cortex in monkey.

There is much evidence that this transthalamic pathway is functional. Unit responses to olfactory bulb stimuli have been recorded in the neocortex[98, 132] as well as in the thalamic mediodorsal[98, 139] and submedian nuclei[98]. Rats with lesions of mediodorsal nucleus show deficits when required to discriminate between similar odors[17] and when odor stimulus reversals are tested[126]. Lesions of olfactory neocortical regions also produce discrimination deficits[17, 132].

Centrifugal system

The centrifugal inputs to the olfactory bulb have been recently reviewed[58]. They arise from many, but not all, of the olfactory terminal regions and from other areas, including the locus coeruleus, raphe nuclei, and the nucleus of the horizontal limb of the diagonal band. The distributions of these centrifugal systems within the olfactory bulb are of particular interest here, because they might provide routes for certain central regions to independently influence subsets of the sublaminae of the EPL or of interneurons within the periglomerular region. One prominent centrifugal input is from the nucleus of the horizontal limb of the diagonal band (NHDB). The heaviest projections of these cholinergic fibers are to the internal plexiform layer and the glomerular layer[59]. They also innervate granule cell spines of the EPL[94, 96].

The centrifugal inputs from piriform cortex and anterior olfactory nucleus also have a laminar terminal arrangement. The posterior piriform cortex of the rat and hamster project predominantly to the deep portion of the granule cell layer[11, 53]. These reports disagree on the projections from the anterior piriform cortex, with observations on the rat[53] indicating projection to deep granule layer and observations on the hamster indicating projection to superficial granule layer with some EPL label[11]. The pars externa of the AON projects to the superficial part of the granule layer of the contralateral olfactory bulb in a topographic manner, corresponding to its input from the ipsilateral bulb[11, 53]. The ventroposterior part of AON projects bilaterally to the olfactory bulb with concentration in the superficial granule layer and in the deep periglomerular layer, while the pars medialis of the AON projects ipsilaterally to the deep part of the granule layer[11, 53]. Evidence from antidromic stimulation[72] and double label fluorescence retrograde transport experiments[1] show that some AON cells send collateral projections to both olfactory bulbs. The AON projection through the anterior commissure has been studied physiologically and demonstrated to have inhibitory influence on presumed mitral cells[74].

Functional overview

There is no comprehensive theory of central mechanisms in olfactory coding. There have been speculations about mechanisms that might avoid the requirement of topographic organization in the bulbocortical projection. For example, Macrides[56, 57] has observed temporal patterns of odor response that varied with the odor being tested and speculated that these patterns might serve as a central code. He suggested that the temporal patterns arise because of the differential spatial distribution of odor sensitivity in the receptor epithelium. The theta rhythm of the olfactory bulb and other forebrain structures is synchronized with the sniffing of the animal during an odor learning task[60] and may be used as an internal temporal standard to decode the temporal patterns of activity. This hypothesis, however, must deal with observations that the temporal patterns of odor responses change with odor concentration as well as with odor quality[42, 64].

In another approach, Freeman has taken as his data set the 'bursts' of induced waves of the olfactory bulb generated during sniffing in alert animals. The EEG recorded simultaneously from multiple sites on the olfactory bulb shows gradients of voltage that vary with conditions such as familarity or odor training, but not with odor[23]. These data suggest a strong influence of the centrifugal systems on olfactory processing. Freeman interprets these patterns as 'expectation' rather than as a strictly sensory response. This type of analysis offers great advantage for sampling the spatial distribution of neural activity in the bulb or cortex but does not allow evaluation of which particular subgroups of local circuits summarized in this review are involved.

Haberly and Bower[29] have also suggested that the lack of topography in the bulbocortical projections should encourage investigation of ensemble processing. They also point out that, while most other sensory systems have strong topographic components, the components of these systems involved in higher processing do not appear to be topographically organized. This is to be expected since, for example, there are patterns of visual and auditory input that can be recognized independently of their specific points of stimulation on the receptor surface.

The piriform cortex is not morphologically homogeneous and probably varies in its function. The regions of the cortex differ in the amount of tufted cell input and, while the bulbocortical projection is not topographic, there are tendencies for certain neurons (on both a population[113] and individual basis[84, 114]) to project their axons to particular parts of the cortex.

The function of piriform cortex itself is not established. LOT lesions that should have denervated most of the piriform cortex did not have significant effects on simple odor detection tasks[125], while neocortical olfactory lesions have effects on more subtle olfactory tasks. While the piriform cortex and olfactory tubercle provide afferents to the olfactory neocortex, their role in determining the response properties of neocortical cells has not been seriously investigated.

Several reports have emphasized differential projections and differential responsivity of mitral and tufted cells. It is unlikely that this anterior-to-posterior gradient of tufted cell projections is the basis of transmission of information about odor quality, because the number of projection cell types is too small, and because the 2-deoxyglucose data[9, 40, 123, 128] indicate that sensitivity to odor quality is organized tangentially in the bulb rather than in layers. Nevertheless, the potential organization of the bulb output into parallel paths filtering sensory information by different principles may be very important in the projection as in other sensory systems[16, 129, 130, 133]. Slotnick presented behavioral indications that large areas of the piriform cortex may not be important for odor discrimination. Anatomical evidence suggests that the part of piriform cortex receiving only mitral cell projections may maintain its association[31, 53] and centrifugal[11, 53] connections distinct from other areas receiving tufted cell projections. It is not clear to what extent the neocortical projection comes from the exclusively mitral cell projection, and the amount of overlap of mitral and tufted projection to some anterior regions is not known. Evaluation of this potential parallel organization may be one of the growing themes in the study of the olfactory bulb connections. Progress will require new structural and functional information on the central projection areas as well as detailed studies of mitral and tufted cell responses to sensory stimuli.

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Chemical communication in invertebrates

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Chemical communication is pervasive in nature

In these modern times one feels relatively secure in stating that all biological events are ultimately chemical events in one form or another. Although it remains risky to attempt a similarly facile description of the symmetry breaking physical events which originally gave rise to the dynamic patterns and nonequilibrium states which define life's processes, it is clear that: living, better or otherwise, is chemistry. Thus the synthesis, transport, detection, utilization and storage of chemical compounds are essential capabilities of living organisms. In a similar vein, it is apparent that all of the organizing transformations which distinguish living matter, at whatever level of biological complexity one may wish to consider, require systems for the generation, transmission, reception, processing and storage of information. This capability to utilize information and to sustain its incessant flux between and within the various compartments of a living system determines and supports nature's emergent properties[17,29].

The animated communication systems found in nature have evolved to satisfy an enormous range of need and purpose. They vary widely in the media and mechanisms used for signaling and in the relative immutability of their messages both in time and in space. For example, a detailed set of instructions for the assembly of a complete individual is contained in the genetic material found in each of the component cells of an organism. This genetic information is coded directly in the complex chemical structure of the DNA molecule, where it is faithfully transmitted again and again over the course of evolutionary time[25]. Communicative features are also readily apparent in the detection and recognition of antigens by individual lymphocytes and in the subsequent conversion of the lymphocyte into a blast cell which can produce a whole new colony of cells each with a specific set of detectors for recognizing the original antigenic signal[33,41]. The evolution of creatures with discrete nervous systems, wherein chemical and electrical signals mediate, coordinate and modulate life's myriad component stages is an obvious example of the development of specialized biological communication systems which gather together into a unified structure many of the available modes of information transfer required for efficient communication both within and between individuals. This developmental process culminates in the appearance of human intellect and language with their profound effects on the organization and regulation of human behavior.

Chemical compounds can be tailored in a seemingly endless variety of ways to produce chemical signals with a wide variety of spatial and temporal properties. It is not too surprising therefore to find that the common problems on inter- and intra-specific communication have been met most often with the tools already at hand, and have resulted in the frequent evolution of chemical communication systems. These systems range from the generalized ability of the *E. coli* bacillus to respond chemotactically to a wide variety of different environmental chemicals[1,20], to the more specialized communication between pre- and post-synaptic membranes in the vertebrate neuromuscular junction which utilizes a relatively small number of specific chemical messengers[28].

Chemical communication system design

It is a generally accepted principle that the evolutionary significance of a particular message is positively corre-