6 Neurochemistry of the Main Olfactory System

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Abstract: Many aspects of animal and human behavior are guided by, or dependent on, the sense of smell-olfaction. This chapter summarizes the major facts of the anatomy, neurochemistry, molecular biology and physiology of the olfactory system. We emphasize the mammalian olfactory system, particularly rodents, because of their widespread use as a laboratory model and the rich database related to this species.

List of Abbreviations: 5-HT, serotonin; 6-OHDA, 6-hydroxydopamine; AChE, acetylcholinesterase; ACIII, adenylate cyclase type III; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; AOB, accessory olfactory bulb; AON, anterior olfactory nucleus; AP4, 2-amino-4-phosphonobutyric acid; BAPTA, bis (2-aminophenoxy)ethane-N,N,N,N-tetra-acetate; BDNF, brain-derived neurotrophic factor; CaM, calmodulin; cAMP, cyclic adenosine monophosphate; CB, calbindin; CCK, cholecystokinin; ChAT, choline acetyltransferase; CNGs, cyclic nucleotide gated channels; CR, calretinin; CREB, cAMP-response element-binding protein; CRF, corticotropin-releasing factor; DA, dopamine; DB, diagonal band; DBH, dopamine-β-hydroxylase; EM, electron microscopy; ENK, enkephalin; EPL, external plexiform layer; ET, external tufted; GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; GC, granule cell; GCL, granule cell layer; GL, glomerular layer; IAS, intrabulbar association system; IP_3, inositol trisphosphate; IPL, internal plexiform layer; IR, insulin receptor; JG, juxtaglomerular; LC, locus coeruleus; LHRH, leutenizing hormone releasing hormone; LOT, lateral olfactory tract; M, muscarinic; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-related kinase; MCL, mitral cell layer; mGluR, metabotropic glutamate receptor; MOB, main olfactory bulb; NADPH, nicotinamide adenine dinucleotide phosphate; NAG, N-acetyl-aspartyl-glutamate; NDB, nucleus of the horizontal limb of the diagonal band; NE, norepinephrine; NMDA, *N*-methyl D-Aspartate; NPY, neuropeptide Y; OCNC1, olfactory cyclic nucleotide gated channel subunit-1; OMP, olfactory marker protein; ON, olfactory nerve; ONL, olfactory nerve layer; ORN, olfactory receptor neurons; PC, piriform cortex; PG, periglomerular; PKC, protein kinase C; POC, primary olfactory cortex; PV, parvalbumin; RMS, rostral migratory stream; RNA, ribonucleic acid; SA, short axon; SP, substance P; SSA, superficial short axon; TH, tyrosine hydroxylase; TRH, thyrotropin-releasing hormone; Trk, tropomyosin related kinase; VG, Van Gehuchten; VIP, vasoactive intestinal polypeptide

1 Introduction

The olfactory system consists of two parallel systems, the main olfactory system and the accessory olfactory system. This chapter focuses on the main olfactory system in mammals, specifically on the main olfactory bulb (MOB) and primary olfactory cortex (POC), and it emphasizes the neuroanatomy, neurochemistry, and neurophysiology of these regions in rodents. The sense of olfaction is critically important for food consumption, emotional responses, aggression, maternal and reproductive functions, neuroendocrine regulation, and the recognition of conspecifics, predators, and prey. In many species, olfaction plays a more pivotal role in these functions than in humans, with olfactory cues exceeding visual or auditory cues in importance. The olfactory system has long been an attractive model to study cellular mechanisms underlying the encoding, transfer, processing, and decoding of sensory information. Recent interest in this area has been sparked by a series of dramatic breakthroughs over the past decade in our understanding of the organization and function of the peripheral olfactory system, cloning of the olfactory receptors, and identification of the olfactory transduction machinery (Breer, 2003). These advances, together with a wealth of accumulated knowledge about the anatomy and connectivity of the MOB (Shipley et al., 1996, 2004; Shepherd et al., 2004), have set the stage for experiments aimed at unraveling the mechanisms of early sensory processing by bulbar and cortical circuits.

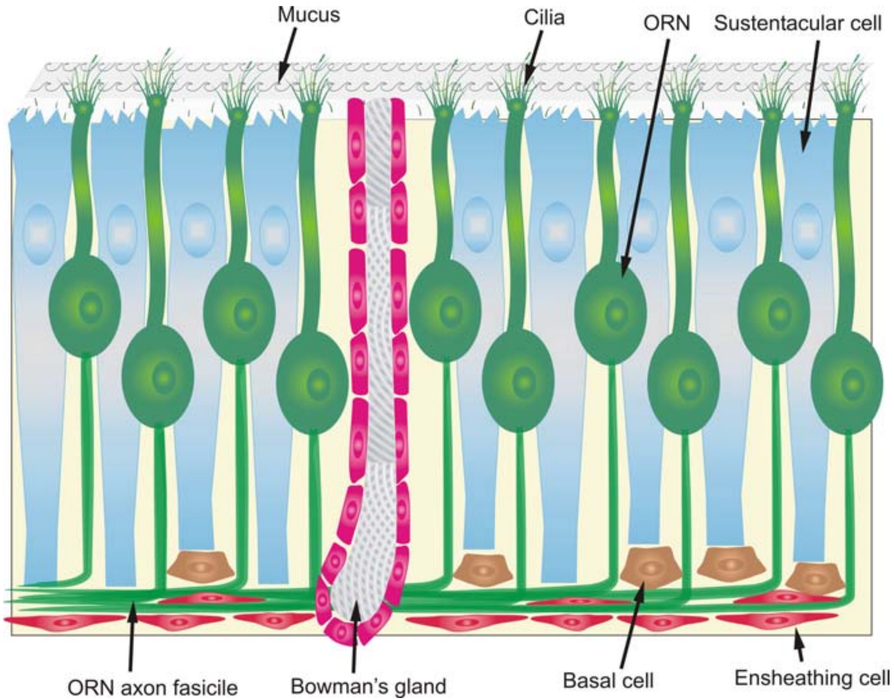
2 The Olfactory Epithelium

2.1 Organization and Cell Types

Odor molecules that enter the nasal cavities and bind to first-order neurons, olfactory receptor neurons (ORNs), which are contained in a neuroepithelial sheet lining the upper and caudal aspects of the nasal

septum and the cribriform plate region of the nasal cavities. ORNs are located in a specific portion of the nasal epithelium, the olfactory neuroepithelium, which is thicker than the surrounding respiratory epithelium and contains a number of distinct cell types (*Figure 6-1*).

Figure 6-1
The olfactory epithelium showing the organization of the olfactory receptor neurons (ORNs) and other cell types



2.1.1 Microvillar Cells and Sustentacular Cells

As the name suggests, microvillar cells (not shown) have superficial microvilli in contact with the mucus (Moran et al., 1982; Muller and Marc, 1984; Rowley et al., 1989; Morrison and Costanzo, 1990). They lie deep within the neuroepithelium and extend an "axon-like" projection, which can reach the MOB, as suggested by tract-tracing studies (Rowley et al., 1989). Sustentacular cells separate and partially wrap the ORNs. Like the microvillar cells, their surface contains microvilli that project into the mucus layer. They may function in mucus composition regulation (Getchell et al., 1984; Getchell and Getchell, 1992). As they express molecules of the P450 enzyme systems (Hadley and Dahl, 1982), they may play a role in detoxification.

2.1.2 Basal Cells

The basal cells are deeply located globose- and horizontal-type stem cells for the replacement of the ORNs (Cuschieri and Bannister, 1975a, b; Graziadei and Graziadei, 1979), which in rodents have a life span of approximately 40 days.

2.1.3 Olfactory Receptor Neurons

ORNs are bipolar sensory neurons with both an apical dendrite and a deep or basal axon (Cajal, 1911a, b). The dendrites extend superficially, forming an olfactory knob with multiple cilia extending into the mucus (Menco, 1984; Menco and Farbman, 1985a, b). Odor transduction takes place in the cilia. Basally, the ORNs give rise to axons—the olfactory nerve (ON) fibers. The axons are ensheathed by specialized Schwann cells, the ensheathing cells (DeLorenzo, 1957). These fibers form bundles, which then collect as groups of fascicles, pass through the cribriform plate, and synapse in the MOB.

2.1.3.1 Neurochemistry of ORNs

Olfactory Marker Protein ORNs express high levels of olfactory marker protein (OMP), which is unique in the olfactory system to ORNs (Margolis, 1972; Keller and Margolis, 1975). OMP is found in a number of mammalian species and it appears to be expressed in all mature ORNs. Studies in mice containing a null mutation for OMP suggest that this protein may play a role in ORN adaptation to odors (Ivic et al., 2000), signal amplification, and transduction (Youngentob et al., 2004).

Glutamate, Carnosine, Copper, and Zinc ORNs contain glutamate and glutamate antibodies stain ON fibers and axon terminals in the glomerular layer (GL) (Liu et al., 1989; Sassoè-Pognetto et al., 1993). Carnosine, a soluble dipeptide, is uniquely expressed in high concentrations in mammalian ORNs, and it is present in ON axon terminals in the GL (Ferriero and Margolis, 1975; Margolis, 1980; Biffo et al., 1990). Carnosine colocalizes with glutamate in the ON axon terminals (Sassoè-Pognetto et al., 1993), and it satisfies criteria for neurotransmitter candidacy, including (1) carnosine synthetic and degradative enzymes are present in ORNs, (2) the peptide is released by depolarization in a Ca^{2+}-dependent manner in ON synaptosomes, and (3) high affinity binding sites for carnosine are present in the GL (Ferriero and Margolis, 1975; Margolis, 1980; Burd et al., 1982; Rochel and Margolis, 1982; Margolis et al., 1983, 1985, 1987; Margolis and Grillo, 1984; Biffo et al., 1990). Zinc and copper are also present in high concentrations in ON axon terminals (Biffo et al., 1990). The potential neuromodulatory roles of carnosine, zinc, and copper are discussed later.

2.2 Odor Receptors, Transduction, and Physiology of ORNs

The binding of odors to receptors located on the cilia of ORNs elicits electrical signals (see Reed, 1992 for review). Olfactory receptors comprise a family of approximately 1,000 G-protein coupled receptors with 7 transmembrane domains that correspond to roughly 1,000 genes. Each mammalian ORN seems to express only a single receptor gene and approximately 10,000 ORNs express the same receptor, although there may be some exceptions (Rawson et al., 2000). The ~10,000 ORNs expressing the same receptor gene are scattered across one of the four epithelial expression zones (Buck and Axel, 1991; Ressler et al., 1993; Vassar et al., 1993; Strotmann et al., 1994; Sullivan et al., 1995). As discussed in *Section 2.3*, collections of ORNs expressing the same receptor project focally onto very few glomeruli in the MOB. Biochemical and electrophysiological studies suggest that the cAMP signal transduction pathway predominates in mammalian ORNs (Schild and Restrepo, 1998; Firestein, 2001; Zufall and Munger, 2001). Odors activate a G-protein, G_{olf}, which activates adenylate cyclase type III (ACIII), leading to a rise in cyclic nucleotide levels (i.e., cAMP). cAMP binds to, and opens, cyclic nucleotide gated channels (CNGs) (Zufall et al., 1991). These channels are permeable to Na^{+}, K^{+}, and Ca^{2+} (Frings et al., 1995). The channels are preferentially permeable to Ca^{2+}, and their activation increases intracellular Ca^{2+} within the cilia (Leinders-Zufall et al., 1997, 1998). Increased Ca^{2+} leads, in turn, to activation of a Ca^{2+}-activated chloride conductance (Kleene and Gesteland, 1991; Lowe and Gold, 1993), which further depolarizes the cell (due to high intracellular Cl^{-} levels relative to the mucus), leading to the generation of action potentials that propagate down the axon to the MOB. Genetic null mutations for G_{olf} (Belluscio et al., 1998), CNGA2 subunits (also called OCNC1) (Brunet et al., 1996), and ACIII (Wong et al., 2000) firmly establish the essential role for these molecules in odor transduction. Mice with null mutations for any of these three transduction elements are functionally anosmic. The transduction process is negatively regulated via several mechanisms, allowing for relatively

rapid adaptation of odor responses. Increased intracellular Ca^{2+} triggers adaptation, as demonstrated by reduced adaptation when intracellular Ca^{2+} is chelated by BAPTA (Leinders-Zufall et al., 1998, 1999). The rise in intracellular Ca^{2+} activates calmodulin, which binds to CNGs, thereby decreasing their affinity for cAMP. The CNGA4 subunits are especially important for this mechanism of adaptation (Bradley et al., 2001; Munger et al., 2001). Ca^{2+}-calmodulin has also been shown to activate CaM kinase II, leading to phosphorylation of ACIII and reduced production of cAMP. CaM kinase II phosphorylates phosphodiesterase, thus increasing inactivation of cAMP. Finally, there is tonic inhibition of CNGs by extracellular Ca^{2+}, which is quite high in mucus, perhaps serving to increase the ORN signal-to-noise ratio (Zufall and Firestein, 1993).

2.3 Topography of ORN Projections to MOB

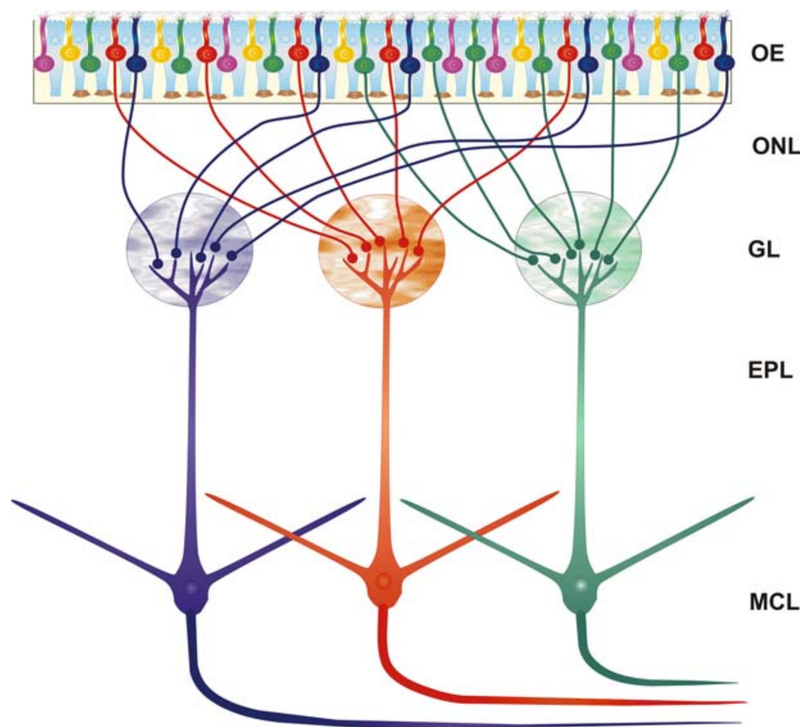
The ORNs of each olfactory epithelium give rise to several million axons that coalesce in the ON layer (ONL) of the ipsilateral MOB and synapse within the glomeruli (Meisami, 1989). Because of the widespread epithelial distribution of ORNs expressing the same receptor, each glomerulus in the MOB receives input from widely dispersed ORNs. In the same manner, adjacent ORNs may project to spatially distant glomeruli (Astic and Saucier, 1986; Saucier and Astic, 1986; Astic et al., 1987; Clancy et al., 1994; Schoenfeld et al., 1994). Early mapping studies showed that there is a crude topography such that ORNs located in the four expression zones project to homologous regions of MOB (Astic and Saucier, 1986; Saucier and Astic, 1986; Clancy et al., 1994; Schoenfeld et al., 1994). The mRNA for the receptor genes is orthogradely transported along ORN axons to their axon terminals. This property led to the discovery that despite the scattered distribution of ORNs expressing the same receptor within the epithelial zones, there is a remarkably precise topographic projection of ORNs expressing the same receptor. Specifically, the ORNs expressing the same receptor project to one or two glomeruli located on the medial and lateral side of each MOB (*Figure 6-2*) (Ressler et al., 1993, 1994; Vassar et al., 1994; Mombaerts et al., 1996; Wang et al., 1998; Potter et al., 2001; Treloar et al., 2002). Studies in transgenic animals showed that this projection pattern is topographically fixed across animals. That is, the same glomeruli identified in different mice receive inputs from the same restricted population of ORNs bearing the same receptor (Mombaerts et al., 1996; Wang et al., 1998; Potter et al., 2001; Treloar et al., 2002). Rough calculations confirm an approximately 1:2 ratio between the number of different types of receptors ($\sim$1,000) and the total number of glomeruli ($\sim$1,800) in mice.

The implications of these receptor localization and expression studies for the odor specificity of individual ORNs are still not fully understood. However, experiments suggest that a receptor may recognize a specific ligand or epitope expressed in common by a number of odors, and that the same receptor may respond to several similar epitopes (Krautwurst et al., 1998; Zhao et al., 1998). In turn, this suggests that an ORN expressing the same receptor responds differentially to a family of odorants containing a common epitope, as well as to other odorants containing different, but structurally similar epitopes. In support of this notion, a variety of electrophysiological studies demonstrate that individual ORNs respond with different degrees of excitation to a spectrum of odors (Malnic et al., 1999; Duchamp-Viret et al., 1999; Hamana et al., 2003). Together, these findings imply that an individual odor will activate a distinct pattern of glomerular activity that depends on the number of specific ORN-receptor gene groups activated.

The results of odor mapping studies in the bulb are consistent with the preceding model. Functional studies utilizing 2-deoxyglucose (Jourdan et al., 1980; Astic and Saucier, 1981; Benson et al., 1985; Johnson and Leon, 2000a, b; Johnson et al., 1998), c-fos (Onoda, 1992; Guthrie and Gall, 1995a, b), magnetic resonance imaging (Yang et al., 1998), Ca^{2+} or voltage-sensitive dye imaging (Cinelli et al., 1995; Friedrich and Korshung, 1997; Wachowiak and Cohen, 1999, 2001; Wachowiak et al., 2000), and intrinsic imaging (Rubin and Katz, 1999; Uchida et al., 2000; Belluscio and Katz, 2001; Rubin and Katz, 2001) suggest that low concentrations of single odorants activate a restricted number of glomeruli. Often, several responsive glomeruli are clustered. These studies suggest that different odors activate unique sets of glomeruli that are topographically fixed from animal to animal. Higher odorant concentrations activate larger numbers of glomeruli, probably resulting from activation of additional ORNs that express a different receptor that has a lower affinity for that odorant. These mapping studies suggest that glomeruli are functional modules that

Figure 6-2

The projections of ORNs to the glomerular layer (GL) of the MOB. Note that ORNs expressing different odorant receptor genes (shown as blue, red, or green cells) are interspersed and widely distributed, yet the axons of ORN expressing the same odorant receptor gene converge onto the same glomerulus (or pairs of medial and lateral glomeruli) in the GL (represented as blue, red, or green glomeruli). EPL, external plexiform layer; MCL, mitral cell layer; ONL, olfactory nerve layer



represent a map of the activity of ORNs. As odors typically activate groups of glomeruli, the olfactory network must extract information from such patterns to recognize and distinguish different odors. The MOB is the first component in the olfactory system that performs this neural computation.

3 Main Olfactory Bulb

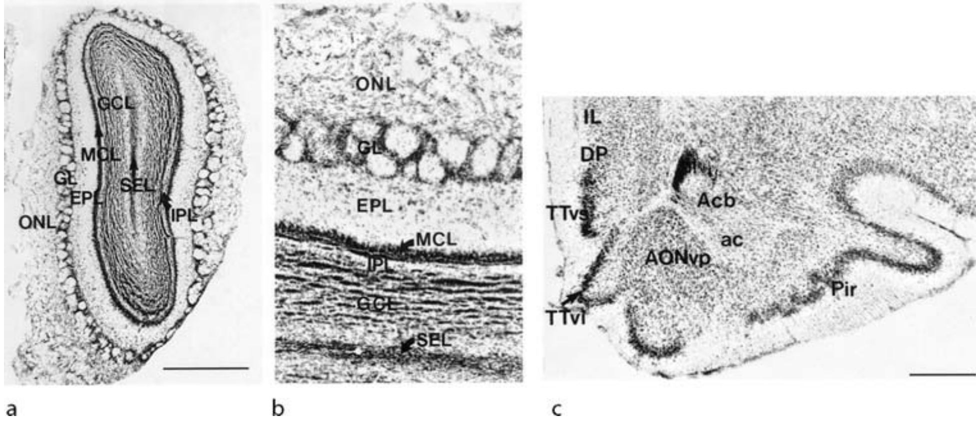
The MOB in rodents is situated at the rostral pole of the cranial cavity and it is connected to the frontal cortex by a slender peduncle. The bulb can be thought of as an elongated onion composed of distinct layers or laminae that are organized as concentric circles. These layers, from superficial to deep, are the ONL, GL, external plexiform layer (EPL), mitral cell layer (MCL), internal plexiform layer (IPL), GC layer (GCL), and the ependymal layer (*Figures 6-3* and *6-4*).

3.1 Olfactory Nerve Layer

The outer and most superficial MOB layer, the olfactory nerve layer (ONL), consists of ON axons and glial cells (Cajal, 1911a, b; Pinching and Powell, 1971b; Doucette, 1989). The glial or ensheathing cells envelop the ON axons and express the Schwann cell marker S100. The deepest third of the ONL also contains

Figure 6-3

Architecture of the MOB (A, B) and primary olfactory cortex (POC, C). A and B: Coronal section (Nissl stain) of the rat MOB at low (A) and high (B) magnifications. C: Coronal section through the rat brain showing several structures of the POC. Abbreviations: ac, anterior commissure; Acb, nucleus accumbens; AONvp, anterior olfactory nucleus, ventroposterior division; DP, dorsal peduncular cortex; IL, infralimbic cortex; Pir, piriform cortex; SEL, subependymal layer; Scale bar in A and C = 1 mm. Modified from Handbook of Chem. Neuroanat. Integrated Sys. CNS, Vol. 12, Part III, Chapter III, The Olfactory System, M. Shipley et al., pp. 469–573, 1996, with permission from Elsevier



astrocytes that reside between bundles of ensheathing cell-wrapped axons (Doucette, 1984; Bailey and Shipley, 1993). Astrocytes in this same region express QPRT, the degradative enzyme for quinolinic acid, an NMDA receptor agonist (Bailey and Shipley, 1993). Quinolinic acid, like glutamate, may modulate glutamatergic transmission between the ON axon terminals and postsynaptic targets. The roles of other neuroactive substances of ORN axons (glutamate, zinc, carnosine), as well as receptors expressed by the ON axon terminals (D2, $GABA_B$), are discussed later.

3.2 Glomerular Layer

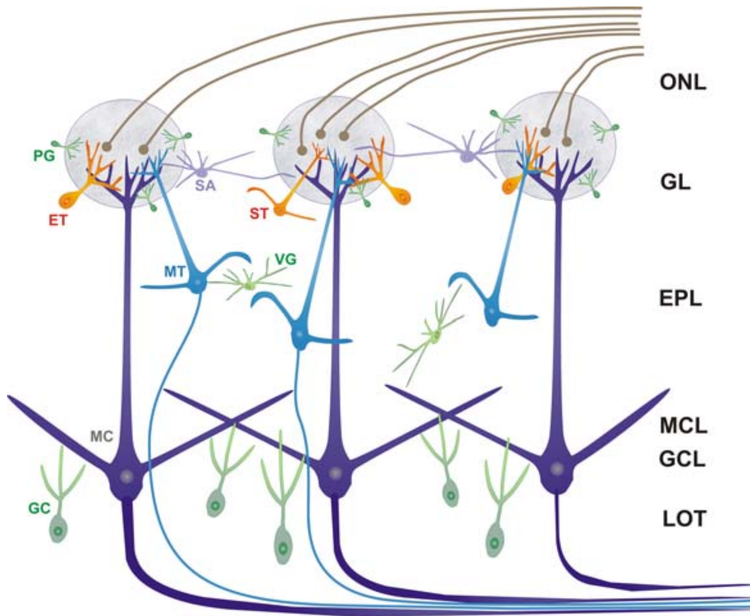
Deep to the ONL, the GL comprises neuropil-rich ovoid structures—the glomeruli—each of which is surrounded by a shell of small neurons and glia. Within the glomeruli, ON axons synapse with mitral and tufted cells, as well as with the intrinsic neurons of the GL. Glomerular diameters are 80–160 μm in rat (Meisami and Safari, 1981; Meisami and Sendera, 1993) and 50–100 μm in mouse (Royet et al., 1988), and the number of glomeruli varies among species: 2000–3000 glomeruli/bulb for rabbits (Allison, 1949); 1800–2000 for mice (Allison, 1953; White, 1972; Royet et al., 1988); 3000 for rats (Meisami and Safari, 1981). More recent stereological studies yielded higher numbers: 6300 glomeruli in rabbit and 4200 in rat (Royet et al., 1998). Adjacent glomeruli are somewhat isolated from each other by astrocytes residing in the glomerular shell. Wedge-shaped astrocytes with somata in the glomerular shell send branched processes into the glomerular core (Bailey and Shipley, 1993; Chao et al., 1997). The astrocytes are restricted to a single glomerulus and they appear to cordon off adjacent glomeruli. This observation provides additional evidence that each glomerulus functions as a discrete unit.

3.2.1 Neuron Types of the GL

The neurons of the GL are classified as three cell types, which include: (1) periglomerular (PG) cells, (2) external tufted (ET) cells, and (3) short axon (SA) cells (Golgi, 1875; Van Gehuchten and Martin, 1891;

Figure 6-4

The basic circuitry of the MOB. Axons of ORNs travel in the ONL and synapse in the GL on the dendrites of mitral cells (MC), tufted cells (external tufted cell, ET; middle tufted cell, MT), and generic juxtaglomerular (JG) neurons, which include periglomerular cells (PG), ET cells, and short axon cells (SA). SA cells interconnect different glomeruli. There are serial and reciprocal synapses between the apical dendrites of mitral/tufted cells and the processes of JG neurons. Superficial tufted cells (ST) are located in the superficial EPL or at the GL–EPL border. The lateral dendrites of mitral/tufted cells form serial and reciprocal synapses with the apical dendrites of granule cells (GC) in the EPL. GCs are located in the GCL and the MCL. The axons of mitral/tufted cells project locally to GCs (not shown) and also to primary olfactory cortex via the lateral olfactory tract (LOT). The bulb also contains other populations of interneurons neurons, including the van Gehuchten cells (VG) within the EPL



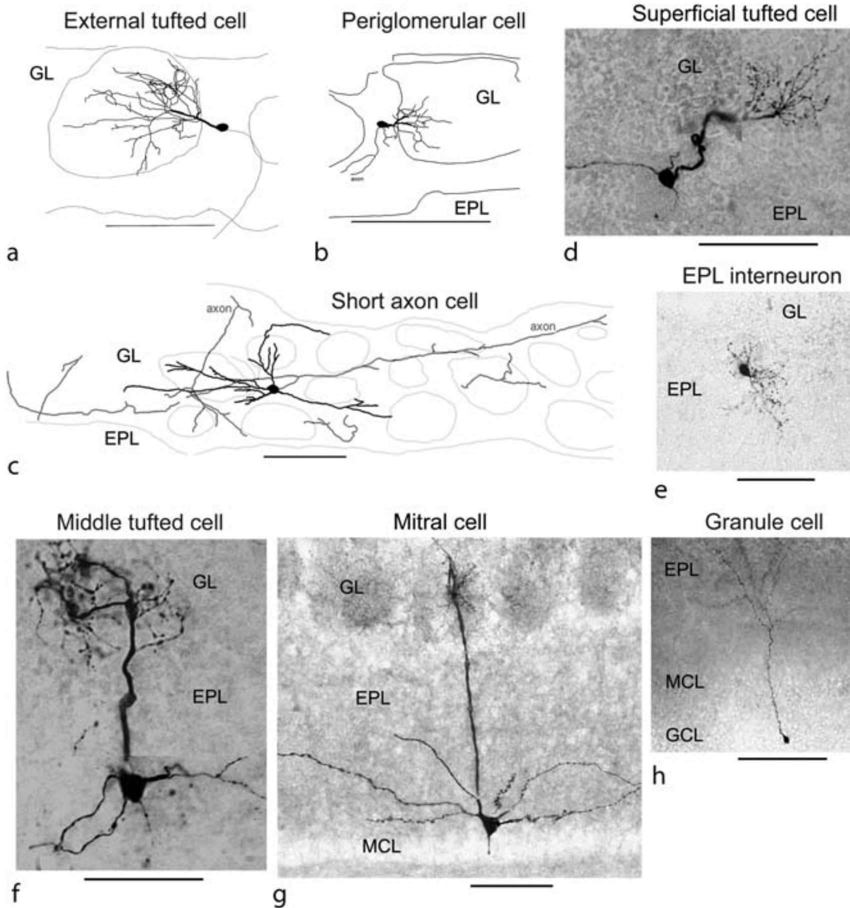
Blanes, 1898; Cajal, 1911a, b; Pinching and Powell, 1971a, b, c; Pinching and Powell, 1972b, c). Collectively, the intrinsic neurons of the GL are referred to as juxtaglomerular (JG) cells. The term JG is also used here with regard to the cited studies in which the subtype of glomerular neuron was not specified. The morphology and features of these cells are illustrated in *Figure 6-5* and are only briefly reviewed here as more detailed descriptions are available (Hayar et al., 2004a, b).

3.2.1.1 ET Cells These are the largest (10–15 µm) cells in the GL, and electrophysiological recordings have confirmed that they are excitatory. They are dispersed in the juxtaglomerular regions, surrounding/deep to the glomeruli. Most have one apical dendrite that arborizes extensively throughout one glomerulus (Pinching and Powell, 1971a; Hayar et al., 2004a, b). Rarely, ET cells have two or three apical dendrites that ramify in different glomeruli. Most ET cells have secondary or lateral dendrites that extend in the superficial EPL. Some ET cells have axons that appear to synapse with PG cells or SA cells, or more infrequently, project out of MOB (Pinching and Powell, 1971a). ET cells are somewhat similar to tufted cells of the EPL and mitral cells, but growing evidence suggests that all tufted cell subtypes exhibit distinct anatomical and physiological properties.

3.2.1.2 PG Cells These cells are the most numerous ones in the GL, and they are thought to be inhibitory in nature. They are small (5–8 µm), spherical or ovoid, and are distributed in the periglomerular regions

Figure 6-5

Neuron types in the MOB. All neurons were labeled in MOB slices by intracellular filling with biocytin during electrophysiological recordings. A–C: Reconstruction of three cells representing the three major types of JG cells in the GL: external tufted cell (A); periglomerular cell (B); short axon cell (C). D−H: Photomicrographs of biocytin-filled superficial tufted (D), EPL interneuron (E), middle tufted cell (F) in the EPL; mitral cell (G, soma in the MCL); granule cell (H, soma in the GCL). Calibration bars in A–H = 100 μm. Figures D−F reprinted from K.A. Hamilton et al., Neuroscience 133: 819−829, 2005, with permission form Elsevier, Ltd



surrounding the glomeruli. Their dendrites are typically restricted to a small subregion of a glomerulus (Pinching and Powell, 1971a; Hayar et al., 2004a, b). These dendrites most commonly receive synapses from axon terminals containing spherical vesicles that have been thought to be collateral branches of ET cell axons and centrifugal fibers (Pinching and Powell, 1971c, 1972c). Other synapses along PG dendrites include asymmetrical (morphologically excitatory) synapses from the ON terminals and from mitral/tufted cell dendrites. Some of the mitral/tufted cell synapses are paired with reciprocal symmetrical (morphologically inhibitory) synapses back onto the parent mitral/tufted cell dendrites (Pinching and Powell, 1971b; Kasowski et al., 1999; Toida et al., 1998, 2000). Physiological recordings indicate that PG cells also receive monosynaptic dendrodendritic excitatory input from ET cells (Hayar et al., 2004b). PG cell axons appear to be rare (Pinching and Powell, 1971a; Hayar et al., 2004a), but they have been reported to extend over distances equivalent to four to five glomeruli. They appear to form symmetrical

(morphologically inhibitory) synapses onto mitral/tufted cell dendrites and ET cells and other JG cells (Pinching and Powell, 1971c).

3.2.1.3 SA Cells These cells are roughly of the same size (8–12 µm) as the ET cells. They are distinguished by multiple dendrites that seem to harvest information from multiple glomeruli (Hayar et al., 2004b). The dendrites may receive synaptic inputs from ET cell dendrites (Hayar et al., 2004b), tufted cell collaterals, or from other SA cells. SA cells have axons that can extend up to 1–2 mm within the GL (Aungst et al., 2003). The axons appear to synapse onto the dendrites of PG cells (Pinching and Powell, 1971a). They do not receive direct ON input (Pinching and Powell, 1971c; Hayar et al., 2004b).

3.2.2 Neurochemistry of JG Neurons

As illustrated in *Tables 6-1* and *6-2*, GL neurons are rich in neuroactive substances and mapping studies have revealed that PG cells in particular are neurochemically heterogeneous (Halász, 1990).

Table 6-1
Neurotransmitters in MOB neurons

Transmitter	Cell type (layer)	References
Aspartate	Mitral	Fuller and Price (1988), Halász (1987), Watanabe and Kawana (1984)
CCK	JG, ET, Tufted, Cajal	Bonnemann et al. (1989), Matsutani et al. (1988), Seroogy et al. (1985)
CRF	Mitral, Tufted	Bassett et al. (1992), Imaki et al. (1989)
DA	JG	Baker et al. (1983,1984,1988), Baker (1986), Gall et al. (1987), Halász et al. (1981), McLean and Shipley (1988)
ENK	PG, Granule, EPL Int,	Bogan et al. (1982), Davis et al. (1982), Kosaka et al. (1995)
GABA	PG, Granule, EPL Int.	Gall et al. (1987), Kosaka et al. (1987d), Mugnaini et al. (1984a, b)
GABA + DA	PG	Kosaka et al. (1985,1988)
GABA + Parvalbumin	Sup. Tufted (EPL)	Kosaka et al. (1987d)
GABA + ENK	Granule	Kosaka et al. (1987d)
GABA and SP and DA	PG	Davis et al. (1982)
Glutamate	JG, Mitral, Tufted	Liu et al. (1989)
NAG	Mitral	Blakely et al. (1987), Ffrench-Mullen et al. (1985)
NADPH-diaphorase	SA (GL), EPL Int.	Alonso et al. (1995), Davis (1991), Scott et al. (1987), Villalba et al. (1989)
Neurotensin	EPL Int.	Matsutani et al. (1988)
NPY	PG, GCL, EPL Int., SA	Briñón et al. (1992), Gall et al. (1986), Nakajima et al. (1996), Ohm et al. (1988), Sanides-Kohlrausch and Wahle (1990a), Scott et al. (1987), Seroogy et al. (1989)
Somatostatin	JG, SA (GL), Deep SA, EPL Int.	Davis et al. (1982), Matsutani et al. (1988), Scott et al. (1987), Seroogy et al. (1989)
SP	JG, Sup. Tufted (EPL), EPL Int.	Baker (1986), Davis et al. (1982), Kream et al. (1984), Wahle et al. (1990)
TRH	PG	Merchenthaler et al. (1988), Tsuruo et al. (1988)
VIP	PG, Sup. Tufted (EPL), Van Gehuchten (EPL)	Crespo et al. (2002), Gall et al. (1986), López-Mascaraque et al. (1989), Sanides-Kohlrausch and Wahle (1990b)

EPL Int., EPL interneuron; Sup. Tufted, superficial tufted cell. Adapted from Handbook of Chem. Neuroanat. Integrated Sys. CNS, Vol. 12, Part III, Chapter III, The Olfactory System, M. Shipley et al., pp. 469–573, 1996, Elsevier, Ltd

Table 6-2
Relative frequency of neurons expressing calcium binding proteins in a 25-μm-thick rat MOB section

Cell Type (Layer/s)	Calcium Binding Protein			
	Neurocalcin	Cabindin D-28k	Calretinin	Parvalbumin
Periglomerular (GL)	+++++	+++++	+++++	++
Sup. Short Axon (GL, EPL)	−	++	+++	++++
Sup. Tufted (EPL)	+++++	−	−	−
Van Gehuchten (EPL)	+	+	++	+++
Mitral (MCL)	−	−	+++	−
Deep Short Axon (MCL/IPL, IPL, GCL)	+	+	+	++
Granule (MCL, IPL, GCL)	++++	−	+++++	+

+++++, more than 500 cells per section; ++++, 250–500 cells per section; +++, 100–250 cells per section; ++, 25–100 cells per section; +, less than 25 cells per section; −, immunonegative. MCL/IPL, IPL border with MCL. Adapted from Briñón etal., J. Comp. Neurol. 407: 404–414 (1999), with permission from John Wiley & Sons, Inc

Electrophysiologically, ET cells appear to be glutamatergic (Hayar et al., 2004b) and they may correspond to JG cells stained by glutamate antibodies (Liu et al., 1989). The GL also contains the largest population of dopamine (DA) containing cells in the brain. The majority of DA containing cells are PG cells, but some ET cells are also dopaminergic (Halász et al., 1977; Davis and Macrides, 1983; Halász et al., 1985; Gall et al., 1986; McLean and Shipley, 1988). Another major neurotransmitter of JG neurons is GABA, which appears to be predominantly contained in PG cells (Ribak et al., 1977; Mugnaini et al., 1984a; Kosaka et al., 1985, 1987a, b, c, d, 1988). Some JG cells that send axons to the deeper GCL contain nicotinamide adenine dinucleotide phosphate (NADPH)-diaphorase, neuropeptide-Y (NPY), and somatostatin, which Scott et al. (1987) suggested may provide a direct route for PG cells to influence granule cells (GCs). Davis (1991) concluded that NADPH in the GL is primarily, if not exclusively, contained in PG cells. The NADPH PG cells are distinct from cells that express calbindin immunoreactivity (Alonso et al., 1993). Other neurotransmitter and neurochemical markers of JG cells include: (1) enkephalin (ENK) (Bogan et al., 1982; Davis et al., 1982; Kosaka et al., 1987d), (2) thyrotropin-releasing hormone (TRH), (Merchenthaler et al., 1988; Tsuruo et al., 1988), (3) acetylcholinesterase (AChE), a marker for cholinoceptive neurons (Nickell and Shipley, 1988b), (4) cholecystokinin (CCK) (Seroogy et al., 1985; Matsutani et al., 1988), (5) aspartic acid (Watanabe and Kawana, 1984; Halász, 1987; Fuller and Price, 1988), (6) vasoactive intestinal polypeptide (VIP) (Gall et al., 1986; Sanides-Kohlrausch and Wahle, 1990a), (7) protein kinase C (Saito et al., 1988) and two Ca^{2+} binding proteins, (8) calretinin (CR) (Jacobowitz and Winsky, 1991; Rogers, 1992), and (9) calbindin-d28k (CB) (Baimbridge and Miller, 1982; Celio, 1990; Briñón et al., 1992).

Three-dimensional analyses using serial-sectioning/mirror-imaging and immunocytochemical double-labeling techniques revealed that about half of the PG cell population can be classified into at least three cell types, including: (1) GABA-positive, (2) CR-positive, and (3) CB-positive (Kosaka et al., 1995, 1998). Moreover, the DA, TRH, and ENK neurons were identified as further subpopulations. About 80% of the DA cells contained GABA in the rat MOB, and in turn, corresponded to about 50% of GABAergic cells (Kosaka et al., 1985, 1987a, c, 1988, 1995; Gall et al., 1987). Therefore, the DA PG neurons are regarded as a subpopulation of GABAergic neurons. Clearly, the neurochemical diversity of JG neurons is remarkable and at present, the role of these neuronal subtypes and their neurochemical constituents in olfactory processing is unclear.

3.2.3 Synaptic and Bicompartmental Organization of the GL

3.2.3.1 Excitatory Systems in the GL In addition to ON axons, each glomerulus contains the apical-dendritic tufts of about 20 mitral cells, 200 tufted cells and 1500–2000 JG cells (Shipley et al., 1996).

Sensory transmission from ON axon terminals is mediated by glutamate acting at AMPA and NMDA ionotropic glutamate receptor subtypes (Bardoni et al., 1996; Ennis et al., 1996, 2001; Aroniadou-Anderjaska et al., 1997; Chen and Shepherd, 1997; Keller et al., 1998). The distribution of these receptors in MOB is discussed later (Section 3.8 and Table 6-3). Electrophysiological studies, described later,

Table 6-3
Neurotransmitter receptors in the MOB

Receptor	GL	EPL	MCL	IPL	GCL	References
Cholinergic						Fonseca et al. (1991a, b), Le Jeune et al. (1996), Rotter et al. (1979), Sahin et al. (1992), Spencer et al. (1986)
M1	–	++	–	++	++	
M2	++	++	++	++	++	
M3	–	++	–	++	–	
M4	–	++	–	++	–	
Nicotinic	++	++	++	–	++	
Noradrenergic						Booze et al. (1989), Day et al. (1997), Domyancic and Morilak (1997), McCune et al. (1993), Nicholas et al. (1993), Palacios and Kuhar (1980), Pieribone et al. (1994), Rosin et al. (1996), Sargent-Jones et al. (1985), Talley et al. (1996), Wanaka et al. (1989), Winzer-Serhan et al. (1997a), Woo and Leon (1995), Young and Kuhar (1980a), Yuan et al. (2003)
$\alpha 1$	++	++	++	++	++	
$\alpha 2$	++	++	++	++	++	
$\beta 1$	++	++	++	–	++	
$\beta 2$	++	–	–	++	++	
Dopaminergic						Coronas et al. (1997), Koster et al. (1999), Mansour et al. (1990a, b), Nickell et al. (1991)
D1	++	–	–	–	–	
D2	++	–	–	–	++	
Serotonergic						Clemett et al. (2000), Cornea-Hebert et al. (1999), Hamada et al. (1998), McLean et al. (1995), Pompeiano et al. (1992, 1994), Tecott et al. (1993), Whitaker-Azmitia et al. (1993), Wright et al. (1995), Yuan et al. (2003)
5-HT_{1A}	++	++	++	++	++	
5-HT_{1C}	–	–	–	–	++	
$5\text{-HT}_{2A/C}$	++	++	++	NR	++	
5-HT_3	++	–	–	–	–	
Glutamatergic						Duvoisin et al. (1995), Gall et al. (1990), Giustetto et al. (1997), Hamilton and Coppola (2003), Kinoshita et al. (1996, 1998), Kinzie et al. (1995, 1997), Martin et al. (1992, 1993), Masu et al. (1991), Miller et al. (1990), Molnar et al. (1993), Monaghan and Cotman (1982), Montague and Greer (1999), Monyer et al. (1994), Ohishi et al. (1993a, b, 1995, 1998), Petralia and Wenthold (1992), Petralia et al. (1994a, b), Romano et al. (1995), Sahara et al. (2001), Sassoè-Pognetto and Ottersen (2000), Saugstad et al. (1997), Shigemoto et al. (1992, 1993), Sun et al. (2000), Tanabe et al. (1992), Van Den Pol (1995), Wada et al. (1998), Watanabe et al. (1993), Wisden and Seeburg (1993)

Table 6-3 (continued)

Receptor	GL	EPL	MCL	IPL	GCL	References
Kainate	–	++	++	++	–	
NMDA	++	++	++	++	++	
AMPA	++	++	++	++	++	
mGlu	++	++	++	++	++	
GABAergic						Bonino et al. (1999), Bowery et al. (1987), Chu et al. (1990), Fritschy et al. (1992), Laurie et al. (1992), Margeta-Mitrovic et al. (1999), Persohn et al. (1992), Richards et al. (1987)
$GABA_A$	++	++	++	–	++	
$GABA_B$	++	–	++	NR	++	
CRF	NR	++	++	NR	++	Chen et al. (2005), Van Pett et al. (2000)

++, receptors present; –, receptors absent; NR, not reported. Adapted from Handbook of Chem. Neuroanat. Integrated Sys. CNS, Vol. 12, Part III, Chapter III, The Olfactory System, M. Shipley, pp. 469–573, 1996, Elsevier, Ltd

have shown that mitral/tufted cells and ET cells are excited by these synapses. ON axon terminals synapse with some subclasses of PG cells, but not with others, and that they do not synapse with SA cells (Hayar et al., 2004a, b; for review see Kosaka et al., 1998). As will also be discussed later, mitral/tufted cells are glutamatergic, and dendritic release of glutamate from these cells has been reported to produce synaptically and nonsynaptically mediated excitation of neighboring cells (i.e., glutamate spillover).

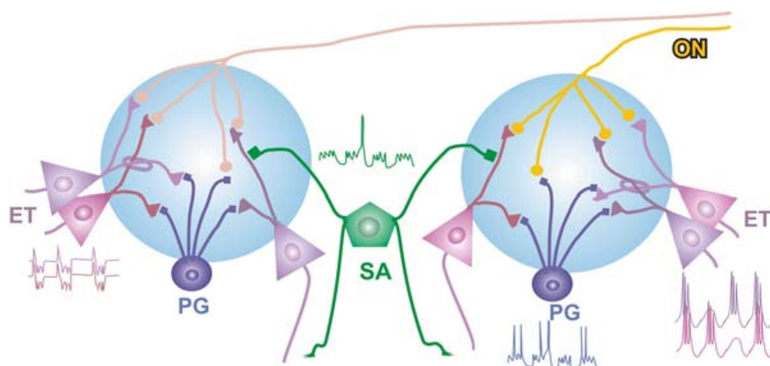
Recent in vitro electrophysiological findings have also provided a new insight into the roles of the different types of JG neurons in olfactory processing (Hayar et al., 2004a, b). Notably, these studies have shown that the spontaneous and sensory-evoked activity patterns of ET cells differ markedly from those of SA and PG cells. ET cells spontaneously generate rhythmic spike bursts and receive monosynaptic ON input, as has also been reported for JG cells in vivo (Getchell and Shepherd, 1975; Wellis and Scott, 1990). SA and PG cells, by contrast, have relatively low levels of spontaneous spike activity, do not possess the intrinsic capacity to generate spike bursts, and mostly respond di- or polysynaptically to ON stimuli. Some dopaminergic PG cells exhibit intrinsic pacemaking activity however (Puopolo et al., 2005). Thus, most SA and PG cells do not appear to receive direct ON input, perhaps because their dendrites ramify in glomerular compartments devoid of ON terminals. Anatomical studies have revealed that the glomeruli have a bicompartmental organization. Each glomerulus has several interdigitating compartments, one of which is rich in ON terminals and the second devoid of ON input (Kosaka et al., 1997; Kasowski et al., 1999). Calbindin-positive JG neurons extend their dendrites only into glomerular compartments devoid of ON terminals, suggesting that they do not receive direct sensory innervation (Toida et al., 1998, 2000). It is reasonable to speculate, therefore, that the SA and PG cells that do not receive direct input (Hayar et al., 2004b) may correspond to these calbindin-positive glomerular interneurons. If most PG cells and all SA cells are devoid of ON input, what circuit mediates their polysynaptic responses to ON stimulation? Recent studies have shown that ET cells, which respond monosynaptically to ON stimulation, in turn relay this input to PG and SA cells (Hayar et al., 2004b). These studies confirmed that ET cells provide direct excitatory glutamatergic input to PG and SA cells. Notably, this microcircuit is intra- versus interglomerular in nature. Mitral/tufted cell dendrites are also likely to provide intraglomerular excitatory input to the PG and SA cells based on anatomical grounds, but this has not been confirmed electrophysiologically (*Figures 6-6).*

3.2.3.2 Inhibitory Systems in the GL

Dendrodendritic Inhibition As noted earlier, PG cells contain GABA and they form inhibitory synapses onto mitral/tufted cell dendrites in the glomeruli. In the periglomerular spaces, their axons also form symmetrical synapses onto the mitral/tufted cell dendrites and PG and SA cells (Pinching and Powell, 1971c). Physiological studies support the notion that PG cells receive excitatory input from mitral/tufted cells and ET cells, and in return, make feedforward and feedback inhibitory GABAergic synapses onto these

Figure 6-6

Intra- and interglomerular circuitry. Glutamatergic ET cells rhythmically burst at sniffing frequencies and receive monosynaptic ON input. ET cells of the same glomerulus burst synchronously and trigger monosynaptic bursts of EPSPs in other JG interneurons (PG and SA cells), most of which do not receive direct ON input. ET cells are synchronized by ON input, glutamate spillover, and interconnections via gap junctions (ovals). ET cells are also synchronized by IPSP bursts from the same and different sets of PG cells. PG cell dendrites ramify in a restricted portion of a single glomerulus and provide local intraglomerular inhibition of ET cells via dendro-dendritic interactions, and also exert presynaptic inhibition of ON terminals. By contrast, SA cells have dendrites and axons extending throughout several glomeruli, and thus might subserve interglomerular interactions (i.e., lateral inhibition). The synchronously bursting ET cell glomerular "ensemble" may constitute an oscillating rhythm generator that monosynaptically synchronizes the activity of PG and SA cells within the same glomerulus, and perhaps also coordinates the activity of mitral/tufted cells via glutamate spillover



cells (Shepherd and Greer, 1998; Hayar et al., 2004b). Such inhibition is thought to be primarily mediated by $GABA_A$ receptors (see *Section 3.8.3*). Because PG cell dendrites ramify within a restricted portion of a glomerulus, their inhibition is presumably localized to microdomains of the extensive mitral/tufted cell dendritic arbors or to nearby JG cells (Kasowski et al., 1999). By contrast to PG cells, SA cells extend dendrites and axons across multiple glomeruli, suggesting that these cells mediate interglomerular functions, such as lateral inhibition of output neurons in neighboring glomeruli (Aungst et al., 2003). The latter study suggests the intriguing possibility that SA cells are excitatory. The possible interactions among ET, PG, and SA cells are illustrated in a simplified network model in *Figure 6-6*. Detailed EM-immunocytochemical work from the Kosaka and Toida laboratories has deduced the synaptic interactions of subclasses of GABA-, DA-, and CB-positive PG neurons with mitral/tufted cell dendrites. A review of this work is beyond the scope of this chapter and interested readers are referred to the original publications (Toida et al., 1998, 2000; Kosaka et al., 2001). PG cells and ET cells also express $GABA_A$ receptors (see *Section 3.8.3*), and there is electrophysiological evidence that some PG cells can release GABA onto themselves, and perhaps neighboring PG cells, in certain circumstances. This occurs through Ca^{2+}-dependent release of GABA (Smith and Jahr, 2002). GABA has been reported to depolarize PG cells at their resting potential, probably due to the elevated intracellular chloride concentrations (Siklos et al., 1995; Smith and Jahr, 2002). It was suggested that GABA inhibits PG cells by activating a chloride conductance that reduces the neuronal input resistance and shunts excitatory inputs. GABA released from PG cells was recently shown to inhibit other PG cells in the same glomerulus via $GABA_A$ receptors (Murphy et al., 2005).

Presynaptic Inhibition of ON Axon Terminals

Dopamine and D2 receptors The GL contains several hundred thousand DA neurons, but the MOB receives no known extrinsic DA input. In mammals, D1 receptor mRNA is expressed in the GL and GCL (Coronas et al., 1997). Immunocytochemical localization of D1 receptors is faint and primarily in the GCL (Levey et al., 1993). By contrast, D1-like ligand binding is present at very low levels in all layers of the MOB

with the exception of the ONL (Mansour et al., 1990a; Nickell et al., 1991; Coronas et al., 1997). The functional significance of D1 receptors in MOB remains unclear. By contrast, only the ONL and GL have high densities of D2 receptors in rats and mice (Mansour et al., 1990a; Nickell et al., 1991; Levey et al., 1993; Coronas et al., 1997; Koster et al., 1999) and to a lesser extent in guinea pigs, but not in cats or monkeys (Camps et al., 1990). In the GL, the JG neurons express D2 receptors (Mansour et al., 1990a). Some immunocytochemical labeling for D2 receptors, as well as in situ hybridization, has been reported in the GCL and EPL, however D2 binding sites are consistently restricted to the ONL and GL (Mansour et al., 1990a; Levey et al., 1993; Coronas et al., 1997). Other anatomical evidence indicates that most, if not all, of the D2 receptors in the GL occur on ON axon terminals. ORNs express D2 receptors and bulbectomy, a manipulation that causes retrograde degeneration of ORNs, eliminates D2 receptor mRNA in the olfactory epithelium (Koster et al., 1999). Taken together, these findings indicate that DA released from JG neurons may presynaptically modulate ON terminals via activation of D2 receptors.

In agreement with this, DA and D2 receptor agonists reduced spontaneous and ON-evoked activity in mitral cells, as well as odor-evoked activity in the GL and odor detection performance, in a variety of species (Nowycky et al., 1983; Doty and Risser, 1989; Sallaz and Jourdan, 1992; Wachowiak and Cohen, 1999; Hsia et al., 1999; Berkowicz and Trombley, 2000; Ennis et al., 2001). These effects are mediated by presynaptic suppression of glutamate release from ON terminals via inhibition of Ca^{2+} influx (Wachowiak and Cohen, 1999). In a similar manner, DA and D2 receptor agonists suppressed spontaneous and ON-evoked activity in JG cells, but had no effect on mitral-to-JG cell transmission (Ennis et al., 2001). The inhibitory effects of DA were abolished in D2 receptor knockout mice (Ennis et al., 2001). Intriguingly, this presynaptic regulation occurs in the absence of conventional anatomical synapses from JG cells to ON terminals. The close proximity of the dendrites of DA-positive and GABA-positive PG cells to ON terminals may facilitate this "nonsynaptic" presynaptic regulation. Further, synaptic vesicles are present in some dendrites opposed to ON axon terminals (Bonino et al., 1999). What role might such presynaptic inhibition serve? One possibility is that presynaptic inhibition of ON terminals by DA provides a mechanism for increasing the range of concentrations that can be processed by MOB neurons: as activity increases in ON terminals, dopaminergic JG cells are more strongly excited. This in turn provides negative feedback to ON terminals reducing the release of glutamate. Such a scheme would effectively increase the dynamic range of information transfer from ORNs to MOB neurons. Interestingly, systemic administration of D2 receptor agonists has been reported to prevent odorant specific 2-dexyglucose patterns in MOB and to reduce odorant detectability (Doty and Risser, 1989; Sallaz and Jourdan, 1992). Related to this question of how DA participates in odor processing is the degree to which these receptors are tonically active in vivo? If, for example, ON terminals are tonically inhibited by DA via D2 receptors, this might serve to filter out weak signals ("noise"). This might sharpen the spatial pattern of active glomeruli, and facilitate the detection of predominant odors. There is experimental support for this possibility. Blockade of D2-like receptors by systemic administration of spiperone increased the number of mitral cells that responded to single or multiple odorants (Wilson and Sullivan, 1995). One interpretation of this study is that reduced D2 presynaptic inhibition of ON terminals increases the odor responsiveness of mitral cells, but does so at the cost of reduced odorant discrimination. Other effects of both D1 and D2 receptor activation have been reported (Duchamp-Viret et al., 1997; Brünig et al., 1999; Davison et al., 2004).

GABA, $GABA_B$ Receptors, and Taurine $GABA_B$ receptors play a presynaptic inhibitory role, apparently very similar to that described for D2 receptors. As noted earlier, GABAergic PG cells represent a large population of GL interneurons. In the rat MOB, the glomeruli have the highest concentration of $GABA_B$ receptors as determined by radioligand binding (Bowery et al., 1987; Chu et al., 1990) and immunohistochemical localization of $GABA_B$ receptor subunits (Margeta-Mitrovic et al., 1999). EM-immunohistochemistry revealed that the dense labeling in the GL is due to the presence of $GABA_B$ receptors on ON terminals and the somata of PG cells (*Table 6-4*) (Bonino et al., 1999). A variety of imaging and electrophysiological studies have provided solid evidence that GABA released from PG neurons presynaptically inhibits glutamate release from ON terminals via activation of these $GABA_B$ receptors (Keller et al., 1998; Wachowiak and Cohen, 1999; Aroniadou-Anderjaska et al., 2000; Palouzier-Paulignan et al., 2002; Murphy et al., 2005). The MOB also contains the highest levels of the putative inhibitory transmitter

Table 6-4
Gap junctions and connexins in the MOB

Layer/Cell Type	Gap Junctions[a]	Connexin mRNA[b]	Connexin Protein[c]	References
MOB			C×36	Rash et al. (2000)
ONL			C×36, 43	Paternostro et al. (1995), Reyher et al. (1991), Teubner et al. (2000), Zhang and Restrepo (2003)
GL			C×36, 43	Belluardo et al. (2000), Christie et al. (2005), Paternostro et al. (1995), Theis et al. (2003), Teubner et al. (2000), Zhang and Restrepo (2003)
JG cells		C×36		Christie et al. (2005)
PG cells		C×36		Kosaka and Kosaka (2003, 2004), Landis et al. (1974)
M/T–PG dendrites	TEM			Kosaka and Kosaka (2003, 2005)
M/T–M/T dendrites	TEM			Christie et al. (2005), Kosaka and Kosaka (2004, 2005), Rash et al. (2005)
M/T-unidentified dendrites	TEM			Kosaka and Kosaka (2003, 2005), Kosaka et al. (2005)
EPL			C×43	Reyher et al. (1991)
Mitral cell proximal dendrites			C×45	Teubner et al. (2000)
Tufted cells (and/or interneurons?)		C×36, 43		Condorelli et al. (1998, 2000), Miragall et al. (1996)
Unidentified cells			C×43	Theis et al. (2003)
Tufted cells-Interneurons	TEM			Kosaka and Kosaka (2003)
M/T-Interneuron dendrites	TEM			Kosaka and Kosaka (2003)
M/T-Unidentified dendrites	TEM			Kosaka and Kosaka (2003)
M/T-GC dendrites	FF			Landis et al. (1974)
EPL/MCL		C×36	C×36, 43	Belluardo et al. (2000)
MCL		C×36	C×36, 43	Belluardo et al. (2000), Christie et al. (2005), Condorelli et al. (2000), Reyher et al. (1991)
Mitral cells	FF	C×36, 43, 45	C×45	Belluardo et al. (2000), Condorelli et al. (1998), Miragall et al. (1996), Paternostro et al. (1995), Theis et al. (2003), Teubner et al. (2000), Zhang and Restrepo (2002)
IPL			C×43	Reyher et al. (1991), Kosaka et al. (2005), Rash et al. (2005)
GCL				
GCs	TEM, FF	C×36	C×43	Christie et al., (2005), Condorelli et al. (1998), Reyher et al. (1991), Kosaka et al. (2005)
Unidentified cells			C×43	Theis (2003)

[a]Standard transmission electron microscopy (TEM) showing junctions between two cell types or freeze-fracture (FF) replica analysis or intramembranous particles
[b]In situ hybridization or nuclease protection assay
[c]Western blots (entire MOB, presumably including AOB), immunocytochemistry (layers) or immunohistochemistry (cells)
Abbreviations: M/T, mitral/tufted

taurine, exceeding concentrations of GABA and glutamate (Collins, 1974; Margolis, 1974; Banay-Schwartz et al., 1989a, b; Ross et al., 1995; Kamisaki et al., 1996). Taurine is found in ON axons, in various neurons, and in astrocytes (Kratskin et al., 2000; Kratskin and Belluzzi, 2002; Pow et al., 2002). In the ON terminals and some postsynaptic dendrites, taurine is colocalized with glutamate (Didier et al., 1994). Observation of spontaneous taurine release from MOB synaptosomes suggests that taurine may be abundantly released (Kamisaki et al., 1996). In electrophysiological recordings, taurine directly activated presynaptic $GABA_B$ receptors and inhibited ON terminals, and also induced Cl^- currents in mitral/tufted cells. Surprisingly, taurine had no direct effect on PG cells (Belluzzi et al., 2003).

3.2.3.3 Neuromodulation in the GL Neuromodulatory systems in the GL include carnosine and certain heavy metals (copper and zinc), metabotropic glutamate receptors (mGluRs), and neuromodulatory inputs from centrifugal afferents. mGluRs and centrifugal inputs are discussed later (*Sections 3.8.2* and *3.9*). Carnosine, a dipeptide synthesized by ORNs, is localized in ON terminals in the GL and fulfils many criteria for neurotransmitter candidacy. However, no direct postsynaptic actions of carnosine have been revealed to date (MacLeod and Straughan, 1979; Nicoll and Alger, 1980; Frosch and Dichter, 1982; Trombley et al., 1998). Carnosine did not affect currents evoked by glutamate, GABA, or glycine in cultured MOB neurons (Trombley et al., 1998). Because carnosine is a chelator of both zinc and copper, it has been suggested that it might modulate transmission at ON synapses by regulating zinc and copper. Depending on the concentration, both zinc and copper can augment or block responses mediated by NMDA and GABA receptors. Both zinc and copper inhibit NMDA and GABA receptor-mediated currents and synaptic transmission in MOB neurons (Trombley and Shepherd, 1996; Trombley et al., 1998). Carnosine prevented the action of copper and reduced the effect of zinc. These results suggest that carnosine may indirectly influence glutamate actions on MOB neurons by modulating the effects of synaptically released zinc and copper. What roles might carnosine, zinc and copper play in olfactory processing? At present, there are no clear answers to this question. Is carnosine, like other peptide transmitters, preferentially released by high frequencies of ON activity? If so, carnosine may be preferentially released during intense odor stimulation. Zinc is known to be preferentially released during high frequency neural activity. There are neurotoxic effects of zinc and copper, and Trombley (Horning etal., 2000) has speculated that carnosine, by preventing the actions of these metals, may serve an important neuroprotective function, perhaps to protect MOB neurons during intense or high frequency activity.

3.3 External Plexiform Layer

The EPL lies beneath or deep to the glomeruli, and it primarily consists of dense neuropil formed by the dendrites of mitral cells and GCs that ascend from the MCL and GCL, respectively. Relative to other MOB layers, the EPL has a low cell density. In Nissl-stained sections, however, it can nevertheless be seen to contain significant numbers of neurons (*Figure 6-3*). These include several subtypes of tufted cells and intrinsic interneurons, which are described later. Because tufted cells are in many aspects similar to mitral cells, and as mitral and tufted cell dendrites cannot be distinguished ultrastructurally, the term mitral/tufted cell is often used when generalizing to these two cell populations. The dominant feature of the EPL is nevertheless the extensive dendrodendritic synapses between mitral/tufted cells and GCs.

3.3.1 Neuron Types of the EPL

3.3.1.1 Tufted Cells Tufted cells are the most numerous cells of the EPL. Like ET cells and mitral cells, tufted cells of the mammalian EPL have one (or rarely several) apical (primary) dendrite(s) ending in a glomerular tuft, hence the name (Cajal, 1890) (*Figure 6-5*). The size of the tufted cell bodies gradually increases from the superficial to the deep EPL (Cajal, 1890; Pinching and Powell, 1971a; Macrides and Schneider, 1982; Orona et al., 1984). Golgi staining and dye injection studies (*Figure 6-5*) have shown that superficial tufted cells tend to have asymmetrical branching patterns, extending sparsely branched

lateral dendrites obliquely to the projection path of the primary dendrites (Macrides and Schneider, 1982; Orona et al., 1984). Middle tufted cells, deep tufted cells, and mitral cells exhibit more symmetrical branching patterns (i.e., shaped like a bishop's miter), with one apical dendrite and tangentially arrayed lateral dendrites (*Figure 6-5*). Tufted cells that closely resemble mitral cells in size have also been referred to as displaced mitral cells (Blanes, 1898), but this term is now generally reserved for the deepest tufted cells located near the MCL (Mori et al., 1983; Kiyoshi et al., 1984; Mori, 1987a, b). Tufted cells utilize glutamate as their principle transmitter (Liu et al., 1989; Christie et al., 2001), but they also stain for a number of other substances (*Table 6-1*). Many superficial tufted cells contain CCK (Seroogy et al., 1985), and they form a topographically organized, reciprocal network (Schoenfeld et al., 1985), which is described in *Section 3.3.2.4*. In the Chinese hamster, many superficial and middle tufted cells are immunoreactive for substance P. The rat has some of these cells, but in other rodents, few if any occur (Baker et al., 1986; Matsutani et al., 1988). The deep EPL of the Syrian hamster has a few NADPH diaphorase-positive tufted cells (Davis, 1991), and it also has a relatively large population of dopaminergic tufted cells (Halász et al., 1981; Baker, 1986; Gall et al., 1987). The latter cells are relatively rare in other rodent species, but are observed in primates (Smith et al., 1991) and amphibians (Boyd and Delaney, 2002). TH-immunoreactive tufted cells do not coexpress GABA, unlike TH-positive PG cells (Gall et al., 1987). As discussed in *Section 3.4*, many mitral/tufted cells are also immunoreactive for corticotropin-releasing factor (CRF) (Imaki et al., 1989; Bassett et al., 1992), and the rodent EPL exhibits a high density of CRF receptors (De Souza et al., 1985).

Axonal projections of middle and deep tufted cells are similar, but not identical, to those of mitral cells (Schoenfeld and Macrides, 1984; Schoenfeld et al., 1985). The local axon collaterals of tufted cells course mainly in the IPL. The projections of tufted cells beyond the MOB terminate densely in the AON and, to a lesser extent, in other rostral olfactory cortical structures (Schoenfeld et al., 1985; Scott, 1986). Few tufted cell axons project into more caudal POC regions.

3.3.1.2 EPL Interneurons The EPL contains anatomically and neurochemically heterogeneous subtypes of intrinsic interneurons. From a functional standpoint, these cells are not well understood. More information on their synaptic interactions is clearly needed to understand the role of these cells in olfactory processing. Their interactions with tufted cells may be particularly important, because tufted cells are thought to comprise a parallel "channel" for transmitting most of the activity from the MOB, separately from the mitral cells (Shepherd et al., 2004). With Golgi staining methods, the EPL was originally described in the cat as containing multipolar neurons having multiple dendrites originating from two poles, but no axons (Van Gehuchten and Martin, 1891). Other interneuron subtypes were subsequently described in other species (for a review, see Halász, 1990). These subtypes include bipolar interneurons with long processes arrayed tangentially to the MCL (horizontal cells) (Valverde, 1965) and multipolar neurons with varicose dendrites, referred to as Van Gehuchten (VG) cells, which occur together with superficial short axon (SSA) cells resembling those of the GL (*Figure 6-5*) (Schneider and Macrides, 1978). VG cells are characterized by several relatively thick primary dendrites that remain in the EPL and axons terminating around mitral and tufted cells. VG cells with smooth dendrites, horizontal cells thought to be equivalent to SSA cells, and small satellite cells with varicose dendrites that envelop small segments of mitral cell dendrites, have been described (López-Mascaraque et al., 1990). Other VG and SA cells typically have varicose dendrites that branch within either the superficial or deep half of the EPL. With parvalbumin (PV) immunostaining however, interneurons with dendrites that are either varicose or relatively smooth have been observed, and some of these interneurons exhibit intermediate branching patterns (Kosaka et al., 1994a, b). Many EPL interneurons stain for GABA (Mugnaini et al., 1984a; Gall et al., 1987; Kosaka et al., 1987d), including some of those identified as VG and SSA cells (Ohm et al., 1990), and are therefore presumed to be inhibitory. Some of the GABA interneurons are also immunoreactive for PV (Kosaka et al., 1987d). As summarized in *Tables 6-1* and *6-2*, EPL interneuron subtypes are neurochemically diverse and stain for (1) NADPH diaphorase (Scott et al., 1987; Villalba et al., 1989; Alonso et al., 1995), (2) AChE (Le Jeune and Jourdan, 1994), (3) SP (Baker, 1986; Wahle et al., 1990), (4) ENK (Bogan et al., 1982; Davis et al., 1982), (5) NPY (Gall et al., 1986; Scott et al., 1987; Seroogy et al., 1989; Sanides-Kohlrausch and Wahle, 1990a), (6 and 7) neurotensin and somatostatin (Matsutani et al., 1988), (8) VIP (Gall et al., 1986; López-Mascaraque et al., 1989;

Sanides-Kohlrausch and Wahle, 1990b; Nakajima et al., 1996), (9) PV (Cielo, 1990; Ohm et al., 1990; Kosaka et al., 1994a, b; Alonso et al., 1995, 1998; Kakuta et al., 1998; Briñón et al., 1999, 2001; Jia and Halpern, 2004), (10) CB, (11) neurocalcin, and (12) CR (Ohm et al., 1991; Briñón et al., 1992, 1999, 2001; Alonso et al., 1995, 1998; Jia and Halpern, 2004).

3.3.2 Circuitry, Synaptology, and Sublaminar Organization of the EPL

3.3.2.1 Overview of EPL Circuitry and Reciprocal Mitral/Tufted Cell—Granule Cell Dendrodendritic Interactions The neuropil of the EPL contains the vertically oriented apical dendrites of mitral/tufted cells ascending to receive monosynaptic ON input in the GL, and laterally oriented secondary dendrites of the mitral/tufted cells. The majority of the synapses of the EPL are between the lateral dendrites of mitral/tufted cells and the dendrites of GCs. Most of the synapses are: (1) asymmetrical synapses from the mitral/tufted cell lateral dendrites onto GC dendrites, and (2) symmetrical synapses from the spines ("gemmules") of GC dendrites onto the mitral/tufted cell lateral dendrites (Price and Powell, 1970b–d). These synapses are mostly reciprocal (Hirata, 1964; Rall et al., 1966; Price and Powell, 1970d; Woolf et al., 1991), and therefore occur in roughly equal proportion (Jackowski et al., 1978). Similar synapses are formed by mitral/tufted cell bodies and GC dendrites. The mitral/tufted cell lateral dendrites are tangentially arrayed relative to the MOB layers and can extend up to ~1–2 mm from the soma (Mori et al., 1983). One mitral/tufted cell can therefore receive feedback inhibition and lateral inhibition mediated by GCs that are excited by other mitral/tufted cells. As detailed knowledge of the functions of these synapses has been derived from studies of mitral cells, they are described in greater detail in *Section 3.4.1.1*. The mitral/tufted cell dendrites also form synapses with intrinsic EPL interneurons. Through the mitral/tufted cells, these EPL interneurons may therefore indirectly receive input related to the overlying glomeruli (Hamilton et al., 2005). The third element of the EPL is an intrabulbar association system (IAS), and the fourth element is the centrifugal afferent input to the EPL from the POC. The interneuron synapses, IAS, and centrifugal inputs are also described separately later.

3.3.2.2 Synaptology of EPL Tufted Cells Tufted cells are, in many respects, similar to mitral cells in terms of synaptology. The dendritic tufts receive monosynaptic input from ON axon terminals and the lateral dendrites synapse with JG cells in the GL and with GC dendrites in the EPL (Shepherd, 1972; Shepherd et al., 2004). Like mitral cells (*see* *Section 3.4*), tufted-to-GC synaptic interactions involve a strong NMDA receptor component (Christie et al., 2001). The lateral extent of tufted cell inhibition is limited to several glomerular widths, however, ~400 µm as opposed to 750 µm for mitral cells in rats (Christie et al., 2001). The weaker lateral inhibition of tufted cells could merely be due to the fact that their lateral dendrites are relatively short (Mori et al., 1983; Orona et al., 1984). However, recent evidence suggests that inhibition from the intrinsic EPL interneurons, not from GCs, tunes the responses of middle tufted cells to odor stimulation (Nagayama et al., 2004).

3.3.2.3 Synaptology of EPL Interneurons The EPL interneurons were originally thought to interact chiefly with GC dendrites (Schneider and Macrides, 1978). However, more recent studies have suggested that they instead interact with mitral/tufted cell dendrites (López-Mascaraque et al., 1990; Nagayama et al., 2004), a view that is supported by ultrastructural studies. Ultrastructural studies have shown that the PV-IR interneurons of the rat EPL receive asymmetrical synapses from mitral/tufted cell bodies and dendrites, and form symmetrical synapses onto the mitral/tufted cells, many of which are reciprocal (Toida et al., 1994, 1996; Crespo et al., 2001). Surprisingly, although the PV-IR interneurons were observed to form frequent contacts with each other, no synapses were observed at the contact points. However, symmetrical synapses from unidentified PV-immunonegative axons were observed on the PV-immunoreactive cell bodies, where they would be expected to shunt the more distal mitral/tufted cell inputs. The PV-immunoreactive interneurons also receive asymmetrical synapses from unidentified axons (Toida et al., 1996), which could be centrifugal afferents. Synapses from centrifugal fibers have been observed on SA cells (Pinching and Powell, 1972a–c). Combined morphological and electrophysiological analyses showed that multipolar

EPL interneurons with highly varicose dendrites are excited polysynaptically by ON stimulation, most likely via input from mitral/tufted cells (Hamilton et al., 2005). The multipolar interneurons exhibit robust spontaneous excitatory synaptic activity mediated by AMPA/kainate receptors, consistent with immunocytochemical staining studies showing that mouse EPL neurons are strongly reactive to the GluR1 AMPA receptor subunit (Petralia and Wenthold, 1992; Giustetto et al., 1997; Montague and Greer, 1999; Hamilton and Coppola, 2003). Similar electrophysiological recordings were obtained from varicose multipolar interneurons in slices from normal mice and from fluorescent cells exhibiting the same morphology in slices from transgenic mice labeled to reveal GABAergic interneurons. The dendrites of the interneurons that were located in the superficial EPL bridged the space below several adjacent glomeruli (*Figure 6-5*). Interneurons located in the deeper zones bridged an equivalent EPL area, which was approximately equal to the glomerular width (Hamilton et al., 2005). This suggests that multipolar EPL interneurons are excited by mitral/tufted cells and may in turn inhibit mitral/tufted cells within EPL domains that are topographically related to pairs of overlying glomeruli.

3.3.2.4 Sublaminar Organization of the EPL As noted earlier, superficial, middle, and deep tufted cells are distinguished by cell body location and size (Cajal, 1890; Pinching and Powell, 1971a; Macrides and Schneider, 1982; Orona et al., 1983). The lateral dendrites of the superficial, middle, and deep tufted cells course within superficial, intermediate, and deep EPL zones, respectively (Scott and Harrison, 1987). Type I and II mitral cell subtypes have also been identified according to the distribution of their lateral dendrites within the deep and intermediate zones, respectively (Kiyoshi et al., 1982; Orona et al., 1984). Electrophysiological recordings have shown that the sensitivity of these tufted cell and mitral cell subtypes to ON stimulation is correlated with the depth of the lateral dendrites within the EPL. The more superficial tufted cells are more easily excited by ON stimulation than the deeper tufted cells, and the type II mitral cells are more easily excited than type I mitral cells (Schneider and Scott, 1983; Wellis et al., 1989; Ezeh et al., 1993). In response to odor stimulation, superficially located tufted cells also exhibit more prolonged excitation than mitral cells (Luo and Katz, 2001). Thus, anatomically distinct mitral/tufted cell subtypes appear to be functionally distinct.

A differential sublaminar distribution is also observed for the dendrites of superficial and deep GCs. The apical dendrites of superficial GCs have very dense spines, and they terminate within both the superficial and deep portions of the EPL. By contrast, apical dendrites of deeper GCs terminate exclusively within the deep EPL (Orona et al., 1983; Greer, 1987). The dendrites of a third GC subtype produce spines predominantly within the superficial EPL (Mori, 1987a, b). Perhaps as a result of these morphological differences, the superficial EPL stains more strongly for glutamic acid decarboxylase (GAD) (Mugnaini et al., 1984b), for the α3 $GABA_A$ receptor subunit (Panzanelli et al., 2005), and for the AMPA receptor subunit, GluR4 (Montague and Greer, 1999). Both the superficial and deep EPL stain faintly for cytochrome oxidase activity, whereas the intermediate EPL stains darkly (Mouradian and Scott, 1988). Together, these observations suggest that morphologically and neurochemically distinct subsets of mitral/tufted cells might synapse with different subsets of GCs and intrinsic interneurons within the superficial and deep EPL sublaminae (Macrides et al., 1985; Mori, 1987a, b).

3.3.2.5 Intrabulbar Association System Many superficial tufted cells do not appear to project beyond the bulb. The axons of these cells contain CCK (Seroogy et al., 1985), and they form a topographically organized, reciprocal network, the IAS, connecting lateral and medial regions of each MOB (Schoenfeld et al., 1985). The axons of the IAS travel through the EPL and MCL to the IPL, where they coalesce into tracts that travel to the opposite side of the bulb and terminate on the apical dendrites of GCs coursing through the IPL en route to the EPL (Liu and Shipley, 1994). The IAS projection exhibits a high degree of point-to-point, topographical organization. As noted in *Section 2.3* earlier, the ORNs which express the same receptor project to one glomerulus in the lateral bulb and to a second glomerulus in the medial bulb (Ressler et al., 1993; Vassar et al., 1994; Mombaerts et al., 1996; Wang et al., 1998). The IAS projections from a single glomerulus preferentially target the IPL deep to the second glomerulus (Belluscio et al., 2002; Lodovichi et al., 2003). Because CCK typically causes membrane depolarization, activation of the CCK tufted cells presumably depolarizes GCs located on the opposite side of the bulb. Thus, the IAS appears to

modulate the activities of subsets of MOB neurons receiving input from ORNs expressing the same receptor, on opposite sides of the MOB.

3.4 Mitral Cell Layer, Mitral/Tufted Cell Synapses, and Neurochemistry

Deep in the EPL is the MCL, a thin layer that contains the somata of mitral cells (25–35 μm diameter, rat) as well as numerous GCs (Cajal, 1911a, b). There are ~40,000 mitral cells (Meisami, 1989) and ~100,000 GCs in the MCL (Frazier and Brunjes, 1988). Thus, mitral cells make up less than 50% of the cells in this layer. Together with tufted cells, mitral cells are the major class of output cells of the bulb. They extend a single apical dendrite through the EPL to the GL, where it arborizes extensively throughout much of a single glomerulus (*Figure 6-5*). There are about 25 mitral cells (and 50 tufted cells) associated with a single glomerulus (Cajal, 1911a, b; Allison, 1953). The apical dendrites are synaptically contacted by ON terminals (Price and Powell, 1970a; Shepherd, 1972). The secondary dendrites of mitral cells may extend upto 2 mm in the EPL and are oriented tangentially, i.e., parallel to the surface of the bulb. Mitral cells have been subdivided into two classes based on the organization of the lateral dendrites as reviewed in detail elsewhere (Orona et al., 1984; Shipley et al., 1996). These lateral dendrites participate in dendrodendritic synapses with dendrites of GCs, as reviewed earlier and later. In addition, they may receive centrifugal axon inputs and inputs from VG EPL interneurons (Jackowski et al., 1978; Toida et al., 1996). Mitral cells give off axon collateral which terminate, within the bulb, in the IPL and GCL (Mori et al., 1983; Price and Powell, 1970c), or exit the MOB and innervate a number of olfactory-related brain regions collectively known as the POC. Projections to POC are discussed later.

3.4.1 Neurochemistry of Mitral Cells

Mitral (and tufted) cells are glutamatergic (Liu et al., 1989; Christie et al., 2001). A few small mitral cells appear to contain aspartate and project to the largest component of POC, piriform cortex (PC) (Fuller and Price, 1988). Another proposed transmitter for mitral cells is N-acetyl-aspartyl-glutamate (NAG) (*Table 6-1*) based on anatomical grounds (Ffrench-Mullen et al., 1985; Blakely et al., 1987), but there has been little neurophysiological support for this notion (Whittemore and Koerner, 1989; see *Section 5.3.1.1*). The neuropeptide CRF has been demonstrated in mitral and some tufted cells using both immunocytochemistry and in situ hybridization in the rat (Imaki et al., 1989; Bassett et al., 1992). CRF fibers were also observed in layer Ia of the PC, consistent with the dense axonal projections of mitral cells to layer Ia of the PC. Mitral cells express type 1 CRF receptor mRNA (Van Pett et al., 2000), and mouse mitral cells also label for a soluble splice variant of the type 2 CRF receptor (Chen et al., 2005). SP mRNA transcripts have been detected in up to one-half of the rat mitral cells (Warden and Young, 1988), but to date no studies using immunocytochemistry have detected SP in mitral cells of any species (Inagaki et al., 1982; Shults et al., 1984; Baker, 1986). Finally, CR, a Ca^{2+}-binding protein, has been shown by immunohistochemistry to be localized in mitral cells (*Table 6-2*) (Jacobowitz and Winsky, 1991). Transmitter candidates for mitral and tufted cells are discussed further in *Section 5.3.1.1.*

3.4.1.1 Glutamate

ON Input As noted earlier, mitral/tufted cell apical dendrites respond to glutamate released from the ON via AMPA and NMDA receptors (Ennis et al., 1996, 2001; Aroniadou-Anderjaska et al., 1997; Chen and Shepherd 1997). The NMDA receptor-mediated response component is of unusually long duration, leading to a late spiking component in response to ON input (Ennis et al., 1996, 2001; Aroniadou-Anderjaska et al., 1997). An mGluR-mediated component of ON-evoked currents in mitral cells also occurs but is typically small under normal conditions (De Saint Jan and Westbrook, 2005; Ennis et al., 2006), yet, as will be discussed later, blockade of these receptors significantly alters ON-evoked spiking.

Self And Neighbor Excitation Electrophysiological studies indicate that mitral and tufted cells have functional ionotropic glutamate autoreceptors that mediate recurrent excitatory interactions among their

apical and lateral dendrites (Isaacson, 1999; Aroniadou-Anderjaska et al., 1999b; Carlson et al., 2000; Schoppa and Westbrook, 2001; Didier et al., 2001; Salin et al., 2001; Urban and Sakmann, 2002). Mitral cell bodies and lateral dendrites have NMDA (Isaacson, 1999; Isaacson and Murphy, 2001), AMPA, and kainate autoreceptors (Lowe, 2003). Ultrastructural studies indicate that NMDA receptors of the lateral dendrites are extrasynaptic (Sassoè-Pognetto et al., 2003). Mitral cell primary dendrites have AMPA autoreceptors (Salin et al., 2001). NMDA autoreceptors on mitral cells increase the firing frequency during prolonged discharges (Friedman and Strowbridge, 2000). Thus, glutamate released from mitral/tufted cell dendrites appears to spillover and excite glutamate receptors on the same cell and on neighboring mitral/tufted cell dendrites. Such excitatory interactions among mitral tufted cell apical dendrites in the glomeruli are thought to synchronize the discharge of mitral cells associated with the same glomerulus (Carlson et al., 2000; Schoppa and Westbrook, 2001).

mGluRs In dissociated rat and frog, MOB culture preparations, Group I mGluRs increased Ca^{2+} release from internal stores in mitral/tufted cells as well as in MOB interneurons (Geiling and Schild, 1996; Carlson et al., 1997), or it depolarized and increased the frequency of miniature excitatory postsynaptic currents (Schoppa and Westbrook, 1997). Other studies indicate that activation of Group III mGluRs with AP4 inhibits Ca^{2+} currents in mitral cells and presynaptically decreases mitral cell-to-GC synaptic transmission (Trombley and Westbrook, 1992). More recent studies in rat and mouse MOB slices demonstrate that activation of mGluR1 directly depolarizes and increases the firing of MCs, and that these effects persist in the presence of blockers of fast synaptic transmission (Heinbockel et al., 2004). The same study showed that mGluR1 induces a voltage-dependent inward current consisting of multiple components sensitive to K^{+} and Ca^{2+} channel blockade and intracellular Ca^{2+} chelation. mGluR1 antagonists also altered mitral cell membrane potential bistability, increasing the duration of the up- and downstates, and substantially attenuated ON-evoked spikes. These findings suggest that endogenous glutamate tonically modulates MC excitability and responsiveness to ON input via activation of mGluR1.

Mitral/Tufted-to-JG and Mitral-to-GC Excitation Glutamate released from mitral/tufted cells, acting at ionotropic receptor subtypes, mediates dendrodendritic transmission at synapses with JG cells and with GCs (Bardoni et al., 1996; Isaacson and Strowbridge, 1998; Schoppa et al., 1998; Aroniadou-Anderjaska et al., 1999a; Chen et al., 2000; Christie et al., 2001). The mitral/tufted-to-GC cell excitation triggers GABA release from the GC dendrites (Isaacson and Strowbridge, 1998; Schoppa et al., 1998; Chen et al., 2000), which inhibits mitral cells via $GABA_A$ receptors (Shepherd, 1972; Jahr and Nicoll, 1982; Schoppa et al., 1998; Chen et al., 2000; see *Section 3.8.3*). Ca^{2+} influx via the NMDA receptor channel is sufficient to trigger GABA release from GCs, and thus, to drive dendrodendritic inhibition of mitral cells (Chen et al., 2000; Halabisky et al., 2000); however, NMDA-evoked depolarization can also trigger GABA release from these cells via activation of voltage-dependent Ca^{2+} channels.

Modulation of Mitral/Tufted-to-Granule Cell Dendrodendritic Interactions mGluRs may also occur at the mitral-to-granule synapses, although their role is unclear. As noted earlier, activation of Group III receptors was reported presynaptically to decrease mitral-to-GC synaptic transmission (Trombley and Westbrook, 1992), and activation of $GABA_B$ receptors has been observed to reduce dendrodendritic inhibition via suppression of GABA release from GCs due to reduction of high voltage-activated Ca^{2+} currents (Isaacson and Vitten, 2003). Although DA has no direct effect on resting membrane properties of mitral/tufted cells (Ennis et al., 2001), activation of D2 receptors was found to reduce glutamate release onto GCs via inhibition of N and/or P/Q high voltage-activated Ca^{2+} channels (Davila et al., 2003; Davison et al., 2004).

3.5 Internal Plexiform Layer and Granule Cell Layer

The IPL is the relatively thin layer that lies deep to the MCL. It has a low density of cells, composed mostly of dendrites derived from GCs and axons derived from mitral/tufted cells and centrifugal sources (discussed later). As noted earlier, the IPL contains a network of CCK-positive axons and terminals, which derive

from CCK-containing tufted cells as part of the IAS (Liu and Shipley, 1994). The major intrinsic cell type in the IPL appears to be the horizontal cell. Horizontal cell dendrites are oriented parallel to the MCL and horizontal cell axons extend into the EPL (Price and Powell, 1970c). Neurocalcin (Bastianelli et al., 1993; Porteros et al., 1996), CB (Briñón et al., 1992), NADPH diaphorase (Alonso et al., 1995), and ENK (Bogan et al., 1982) have been found in these cells. The IPL also contains a few multipolar neurons, which are larger than GCs and express AChE (Carson and Burd, 1980; Nickell and Shipley, 1988b; Le Jeune and Jourdan, 1994).

The GCL is the deepest neuronal layer in the bulb, and it contains the largest number of cells. Most of the neurons of the GCL are the GCs, but there are also small numbers of Golgi cells, Cajal cells, and Blanes cells. As discussed earlier, the GCs are inhibitory GABAergic cells that form dendrodendritic synapses with mitral/tufted cells in the EPL.

3.5.1 Neuron Types of the GCL

3.5.1.1 GCs GCs are axon-less cells with small cell bodies that are mostly tightly packed into row-like aggregates of 3–9 somata (*Figure 6-5*) (Reyher et al., 1991). GC bodies are also found mixed with mitral cell bodies within the MCL, however. Golgi studies indicate that most GCs have a thicker, longer apical dendrite that ramifies within the EPL and shorter basal dendrites that ramify within the GCL. As described earlier, several types of GCs occur, which have different dendritic ramifications within the superficial and deep portions of the EPL. Not all GCs follow this pattern, however. The exceptions include GCs with basal dendrites that project deeper, toward the center of the MOB, and GCs with apical dendrites that do not enter the EPL (Schneider and Macrides, 1978). The superficial and deep GCs can also be distinguished using a variety of staining methods. For example, superficial GCs have more dense spines on their apical dendrites and they stain for the transcription factor Er81 (Stenman et al., 2003), whereas deep GCs stain for Ca^{2+}/calmodulin-dependent kinase IV (Baker et al., 2001). The GC spines are also immunoreactive for Ca^{2+}-camodulin-dependent kinase II, expression of which is developmentally regulated. Because MOB interneurons develop postnatally and are added throughout life, the differential staining of cell bodies in the superficial versus deep GCL could be related to the migration and maturation of interneuron progenitors (see later). One function of the cholinergic input to the MOB appears to be related to the survival of these cells (Cooper-Kuhn et al., 2004), which is influenced by nicotinic receptors containing the β_2 subunit (Mechawar et al., 2004). Subpopulations of GCs are either intensely or lightly immunoreactive for CR (Jacobowitz and Winsky, 1991). GCs and some SA cells are also immunoreactive for methionine-enkephalin (Bogan et al., 1982; Davis et al., 1982), whereas deep SA cells are immunoreactive for somatostatin (Davis et al., 1982). Other possible transmitters of GCs are summarized in *Table 6-1*.

As discussed earlier, GCs are excited by mitral/tufted cells at asymmetrical synapses in the EPL. Most GCs contain GABA (Ribak et al., 1977), which, via $GABA_A$ receptors, inhibits mitral/tufted cells (Shepherd, 1972; Jahr and Nicoll, 1982; Schoppa et al., 1998; Chen et al., 2000) at symmetrical synapses within the EPL. Within both the EPL and GCL, the GCs also receive asymmetrical synapses from a variety of centrifugal afferents, however, which modulate these synaptic interactions. Some of the centrifugal afferents have restricted terminations on the GC bodies and dendritic arbors, suggesting that different sources of centrifugal input could differentially modulate GC synaptic interactions with mitral/tufted cells (Price and Powell, 1970c). In large part, these centrifugal fibers arise from neurons in POC (e.g., PC and AON), which form the bulk of synaptic contacts onto GC somata and proximal dendrites within the GCL (Price and Powell, 1970c). Deep to the EPL, GCs also receive synapses from the collateral branches of mitral and tufted cell axons. During mitral cell excitation, coincident, γ-frequency stimulation of GC proximal dendrites relieves the Mg^{2+} blockade of their NMDA receptors and facilitates recurrent mitral cell inhibition (Halabisky and Strowbridge, 2003), presumably via activation of these axon collaterals. In addition, GCs receive minor inputs from Golgi, Cajal, and Blanes cells (Price and Powell, 1970c) and GCs also receive symmetrical synapses thought to be from the axons of deep SA cells, described later. The SA cells could be a source of GC inhibition as noted earlier. GABAergic centrifugal afferents from the nucleus of the horizontal limb of the diagonal band are another likely source of this inhibition (Kunze et al., 1992).

GCs express high levels of the transient outward potassium current activated by depolarization—the A-type current (Schoppa and Westbrook, 1999). This current plays an important role in dendrodendritic transmission with mitral cells in the sense that it dampens the AMPA-mediated synaptic depolarization of GCs and thereby allows NMDA receptor-mediated depolarization to play a relatively greater role. A-currents may also negatively modulate backpropagation of spikes in GC lateral dendrites (Christie and Westbrook, 2003). As noted earlier, activation of $GABA_B$ receptors on GCs has been reported to reduce GABA release from these cells via inhibition of high voltage-activated Ca^{2+} channels (Isaacson and Vitten, 2003). GCs also receive excitatory glutamatergic projections arising from POC (see *Section 3.7.2.1*). GCs express type 1 and 2 CRF receptor mRNA (Van Pett et al., 2000; Chen et al., 2005).

3.5.1.2 Other Deep Interneurons The deep MOB layers contain several subtypes of SA cells (Price and Powell, 1970b; Schneider and Macrides, 1978; López-Mascaraque et al., 1990). The somata of these cells mostly occur within the IPL and GCL, and they project multiple dendrites and axons that ramify within the EPL, MCL, and GCL. The deep SA cells include horizontal cells, similar to those seen in the EPL, and Cajal cells (Cajal, 1890; Van Gehuchten and Martin, 1891; Blanes, 1898). The Cajal cells, which are also known as vertical cells of Cajal, have fusiform cell bodies that project dendrites perpendicularly rather than tangentially to the MCL. The apical dendrites extend through the MCL into the EPL, the basal dendrites extend into the GCL, and the axons project out of the GCL into the EPL (Cajal, 1911a, b). By contrast, the Blanes cells have numerous dendrites emerging from all sides of the soma. The axons from these cells can extend considerable distances, but they remain within the GCL (Cajal, 1911a, b). Larger Golgi cells (Golgi, 1875) and Blanes cells (Blanes, 1898) occur in the deeper layers. Golgi cell morphology varies considerably, but the dendrites are generally radial and the axons remain within the GCL (Cajal, 1911a, b). The dendrites of all four of these deep interneuron subtypes are varicose, but the Blanes cell dendrites are also densely spiny (Schneider and Macrides, 1978). For a detailed discussion of early literature concerning these cells, see Halász (1990).

Very little is known about the functions of the deep interneurons, but they are presumed to be inhibitory. Their axon terminals have been thought to be a source of the numerous symmetrical synapses observed on the cell bodies, basal dendrites, and spines of GCs (Price and Powell, 1970d), and some types have been shown to be immunoreactive for GABA (Gracia-Llanes et al., 2003). Recent ultrastructural evidence indicates that the VIP-containing deep short-axon cells form symmetrical synapses onto other deep interneurons containing VIP, calbindin, or NPY, but not onto GCs (Gracia-Llanes et al., 2003). Deep interneurons have also been shown to receive asymmetrical synapses that are presumed to be from mitral/tufted cell axon collaterals (Price and Powell, 1970b). It therefore appears that at least some of these interneurons inhibit other deep interneurons in response to their excitation by mitral/tufted cells. As with the more superficial interneurons, however, the deep interneurons are immunoreactive for a rich variety of substances, most notably neuropeptides (*Table 6-1*) and Ca^{2+} binding proteins (*Table 6-2*), suggesting they could serve a variety of functions. Some GCL interneurons contain NPY (Gall et al., 1986; Ohm et al., 1988). These are probably Golgi or Cajal cells, giving rise to axons that ramify in the more superficial layers such as the EPL and GL. Cajal cells stain for NADPH diaphorase, and they are immunoreactive for neurocalcin, CB, and potentially, NPY (Gall et al., 1986; Briñón et al., 1992; Bastianelli et al., 1993; Alonso et al., 1995; Porteros et al., 1996). Blanes cells also stain for NADPH diaphorase, and immunoreactivity for NPY has been observed in a population of "Blanes-like" cells near the ventricular layer (Scott et al., 1987), although the exact identity of these NADPH diaphorase/NPY cells has yet to be confirmed. Recent work shows that Blanes cells mediate persistent monosynaptic GABAergic inhibition of GCS (Pressler and Strowbridge, 2006).

3.6 Subependymal Layer and Rostral Migratory Stream

The deepest layer in the MOB is the subependymal layer (also called subventricular zone), which is a cell-poor region lining the ventricle (if present) in adults. Most MOB interneurons originate postnatally from progenitor cells within this layer (Hinds, 1968; Altman, 1969; Bayer, 1983). In adults, interneurons (primarily GCs and PG cells) are also continually generated from these progenitor cells and their offspring

generated en route migrate to the MOB within the rostral migratory stream (RMS) (Luskin, 1993; Lois and Alvarez-Buylla, 1994; Smith and Luskin, 1998; Wichterle et al., 2001). The RMS progenitors express the ETS transcription factor Er81, and they originate from the lateral ganglionic eminence (Wichterle et al., 2001; Stenman et al., 2003). They continue to migrate and divide in the absence of the bulb (Kirschenbaum et al., 1999), but they only reach their final destinations and mature if the GL and MCL+plexiform layers are present (Liu and Rao, 2003). Recent evidence shows that the extracellular matrix glycoprotein tenascin-R is important to this process (Saghatelyan et al., 2004). Many of the offspring nevertheless die (Kaplan et al., 1985; Brunjes and Armstrong, 1996; Kato et al., 2000), with olfactory stimulation apparently being critical to the survival of new interneurons during development (Frazier-Cierpial and Brunjes, 1989; Corotto et al., 1994; Najbauer and Leon, 1995; Fiske and Brunjes, 2001) and of mature, presumably synaptically connected, interneurons in adults (Petreanu and Alvarez-Buylla, 2002; Hack et al., 2005). Two subsets of new interneurons have been identified, which express either TH, which is required for DA synthesis, or Ca^{2+}-calmodulin-dependent protein kinase IV during migration (Baker et al., 2001). The transcription factors Pax6 and Olig2 play important roles in determining the dopaminergic phenotype of a periglomerular subset of these interneurons (Hack et al., 2005).

Both the progenitors and new interneurons express functional $GABA_A$ receptors. Electrophysiological studies indicate that the new interneurons subsequently express functional AMPA receptors, then NMDA receptors, before they exhibit spiking activity, responses to ON stimulation, and spontaneous glutamatergic EPSCs (Belluzzi et al., 2003; Carleton et al., 2003). These electrophysiological studies provide evidence that the new interneurons become functionally integrated into the MOB circuitry. Neural cell adhesion protein-deficient mice, which exhibit defective migration of new interneurons into the GCL resulting in reduced MOB size, have been shown to exhibit impaired odor discrimination (Gheusi et al., 2000). Although threshold detection and short-term odor memory were normal in these mice, in normal mice both olfactory memory and survival of the new interneurons were improved following rearing in an odor-enriched environment (Rochefort et al., 2002). Thus, the neurons of the subependymal layer and RMS appear to be important both to MOB development and to certain olfactory functions during adulthood.

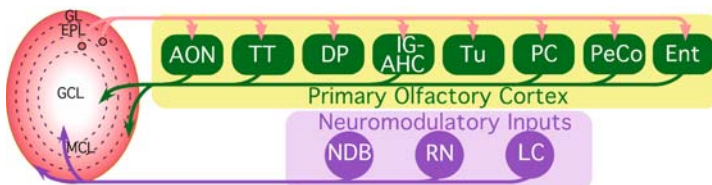
3.7 Outputs and Inputs of the MOB

3.7.1 Outputs of MOB

The output neurons of the MOB are mitral and tufted cells. These cells project to a number of structures collectively designated as the POC (de Olmos et al., 1978). The features of POC, including input from MOB, are described later (*Figure 6-7*).

Figure 6-7

Major connections of the main olfactory system. Axons of MOB mitral/tufted cells (circles in the EPL and MCL, respectively) project as the LOT to synapse in a number of structures collectively referred to as primary olfactory cortex (POC). Centrifugal inputs to MOB include feedback projections from POC as well as inputs from subcortical forebrain and brainstem neuromodulatory cell groups. Abbreviations: AON, anterior olfactory nucleus; DP, dorsal peduncular cortex; Ent, entorhinal cortex; IG-AHC, indusium griseum-anterior hippocampal continuation; LC, locus coeruleus; NDB, nucleus of the diagonal band; PeCo, periamygdaloid cortex; PC, piriform cortex; RN, raphe nuclei (dorsal and median raphe); TT, taenia tecta; Tu, olfactory tubercle



3.7.2 Extrinsic Inputs to MOB

Extrinsic afferent input to MOB, also referred to as centrifugal fibers, can be subdivided into two classes: (1) inputs arising from olfactory-related structures, in particular those arising from POC, and (2) inputs arising from non-olfactory, so-called neuromodulatory transmitter systems including ACh, NE, and 5-HT. The modulatory transmitter systems are considerable and are described in *Section 3.9*.

3.7.2.1 Neurochemistry of POC inputs to MOB Before departing to the MOB, it is germane to consider the neurochemistry of the input to the MOB from POC. As described later, feedback projections to the MOB from POC arise predominantly from glutamatergic, pyramidal neurons in layer II and III of PC, as well as other POC structures. These projections massively target GCs, where they form asymmetrical synapses on the cell bodies, basal dendrites, and spines of GCs (Price and Powell, 1970a). Activation of these feedback projections produces a negative field-potential recorded in the GCL (Walsh, 1959; Nakashima et al., 1978), as expected, if excitatory currents are flowing into GCs. Similar stimulation elicits IPSPs in mitral cells (Yamamoto et al., 1963; Nicoll, 1971; Mori and Takagi, 1978), due to GC excitation and subsequent GABA release (Halász and Shepherd, 1983). The transmitter of these feedback projections to GCs is glutamate. Activation of POC input to MOB excites GCs as measured by voltage-sensitive dye and field-potential recordings in vitro. This excitation is mediated by glutamate acting at both AMPA and NMDA receptors (Laaris and Ennis, 2002). A major function of these projections is to provide an inhibitory regulation of the firing rate and excitability state of mitral/tufted cells. Activation of these inputs modifies (inhibits) odor responses in MOB (Kerr and Hagbarth, 1955; von Baumgarten et al., 1962).

3.8 Amino Acid Receptor and Gap Junction Distribution in MOB

The following sections review the distributions of glutamate and GABA receptors and gap junction proteins in the MOB. In some cases, additional details about the neurophysiology and functional significance of the receptors are provided in the layer-specific sections earlier.

3.8.1 Ionotropic Glutamate Receptors

The three classes of ionotropic glutamate receptors- NMDA, AMPA, and kainate- are distributed extensively throughout the MOB. NMDA receptors are found in every layer of MOB except the IPL (Watanabe et al., 1993; Monyer et al., 1994; Petralia et al., 1994b). AMPA receptors are found in all layers except the ONL and subependymal layer (Molnar et al., 1993; Martin et al., 1993; Petralia and Wenthold, 1992; van den Pol, 1995). Kainate receptors are found in the MCL, EPL, and IPL (Monaghan and Cotman, 1982; Gall et al., 1990; Miller et al., 1990; Wisden and Seeburg, 1993).

3.8.1.1 Distribution in the GL Immunoreactivity for the NR1 NMDA receptor subunit is present at synapses between ON terminals and profiles that mostly appear to be mitral and tufted cell dendrites (Giustetto et al., 1997). JG neurons, including PG cells, also express NMDA NR1 subunit, which is also present at the dendrodendritic synapses with mitral/tufted cells in the glomeruli, as well as at synapses from centrifugal fibers and/or tufted cell collaterals in the periglomerular regions (Giustetto et al., 1997; Montague and Greer, 1999). Immunocytochemical studies show that AMPA receptors are also localized to processes and cell bodies of mitral, tufted, and PG cells (Petralia and Wenthold, 1992; Molnar et al., 1993). JG neurons, including PG cells, express GluR1, GluR2/3, and GluR4 AMPA receptor subunits (Giustetto et al., 1997; Montague and Greer, 1999); GluR4 staining is also associated with glia in the GL. Like NMDA receptors, AMPA receptors are present postsynaptically at synapses formed by ON terminals and at mitral/tufted-to-PG cell dendrodendritic synapses. Thus, NMDA and AMPA subunits are localized to ON-to-mitral/tufted cell synapses and to dendrodendritic synapses in the glomeruli (Giustetto et al., 1997).

3.8.1.2 Distribution in the Deeper Layers In the deeper layers, both mitral and tufted cells express NR1, GluR1, GluR2/3, and GluR4 AMPA receptor subunits, and kainate GluR5/6/7receptor subunits, as indicated by immunohistochemical staining (Giustetto et al., 1997; Montague and Greer, 1999). Additionally, the interneurons of the EPL express GluR1, as do GCs (Giustetto et al., 1997; Montague and Greer, 1999; Hamilton and Coppola, 2003). GCs also express GluR2/3 subunits, but they are weakly immunoreactive for GluR1 and 4 receptor subunits (Montague and Greer, 1999). At the mitral/tufted-to-GC synapses, GluR2/3 and/or GluR1 AMPA receptor subunits are colocalized with NR1 NMDA receptor subunits. The GluR2 and 4 subunits occur in equal proportion as both flip and flop splice variants, whereas GluR1 and 3 subunits occur mostly as flip variants (Horning et al., 2004). In primary cell cultures, AMPA receptors of presumptive interneurons (most likely GCs), desensitize more rapidly and completely than AMPA receptors of presumptive mitral/tufted cells. This could be due to the occurrence of a higher proportion of flip subunits (Blakemore and Trombley, 2003). In dissociated preparations, AMPA receptors of presumptive GCs have also been reported to exhibit limited Ca^{2+} permeability, suggesting that GC AMPA receptors must include GluR2 subunits, which regulate Ca^{2+} permeability (Jardemark et al., 1997). The AMPA receptors of mitral cells and JG cells appear to exhibit Ca^{2+} permeability, however (Blakemore and Trombley, 2005; Ma and Lowe, 2005).

3.8.2 Metabotropic Glutamate Receptors

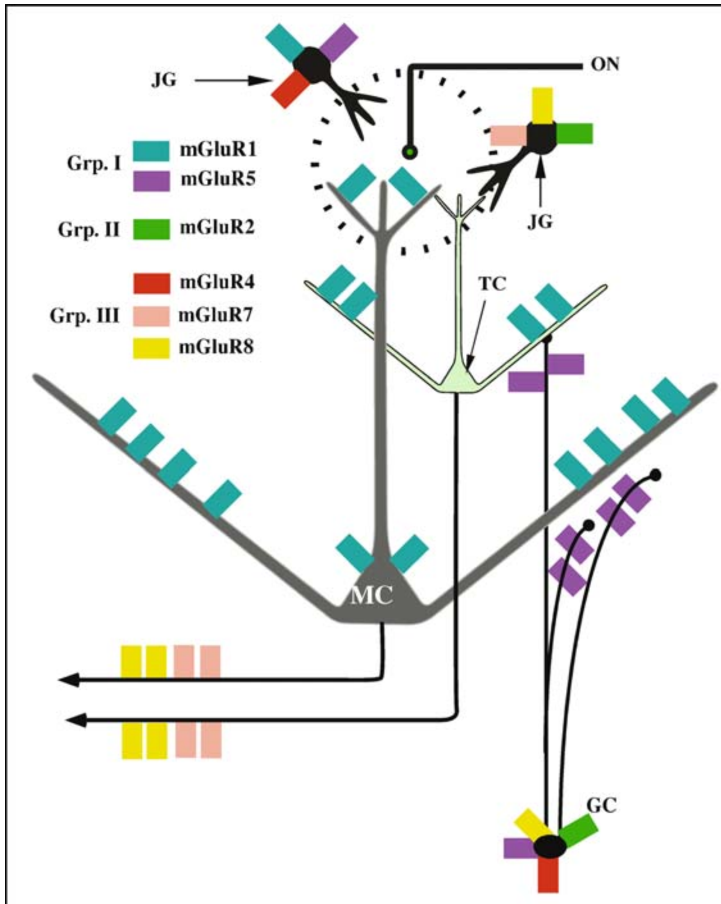
Neuroanatomical studies demonstrate that the MOB expresses high levels of mGluRs, suggesting that these receptors play important roles in olfactory processing. The eight mGluRs identified to date are subdivided into three groups based on sequence homology, signal transduction mechanisms, and pharmacology (Conn and Pin, 1997): Group I mGluRs (mGluR1, mGluR5), Group II mGluRs (mGluR2, mGluR3), and Group III mGluRs (mGluR4, mGluR6-8) (*Figure 6-8*).

3.8.2.1 Distribution in the GL JG cells express several types of mGluRs. Deciphering mGluR expression in the GL from the literature is difficult because mGluR expression has not been systematically examined in the different JG cell types. ET cells appear to have the same mGluR makeup as the deeper mitral/tufted cells; i.e., they express high levels of mGluR1 and lower levels of mGluR7 and mGluR8 (Ohishi et al., 1995; Kinzie et al., 1995; Saugstad et al., 1997). Other, as of yet unidentified JG cells have been reported to express low-to-moderate levels of Group I (mGluR5), Group II (mGluR2), and Group III (mGluR4/7/8) receptors (Ohishi et al., 1993a, 1998; Romano et al., 1995; Saugstad et al., 1997).

3.8.2.2 Distribution in Mitral/Tufted Cells Mitral/tufted cells express high levels of mGluR1 (Masu et al., 1991; Martin et al., 1992; Shigemoto et al., 1992; van den Pol, 1995; Sahara et al., 2001). Electron microscopy studies demonstrated that mGluR1 is present on the somata and apical and lateral dendrites of mitral/tufted cells (van den Pol, 1995). This expression pattern suggests that mGluR1 could mediate mitral/tufted cell responses to glutamatergic inputs from ON terminals, and/or could function as an auto- or heteroreceptor for glutamate released from apical or lateral dendrites of mitral/tufted cells. Mitral/tufted cells also express mRNA for mGluR7 and mGluR8 (Kinzie et al., 1995; Saugstad et al., 1997), although immunocytochemical studies indicate that these receptors are present on mitral/tufted cell axon terminals in the GCL and PC (Kinoshita et al., 1998; Wada et al., 1998). Mitral/tufted cells do not express Group II receptors (mGluR2/3), which contrast markedly with the strong expression of mGluR2 in mitral cells in the Accessory olfactory Bulb (AOB) (Ohishi et al., 1993b, 1998).

3.8.2.3 Distribution in the GCL GCs express the highest levels of mGluR5 (Group I) in the brain (Romano et al., 1995). EM studies have shown that mGluR5 is localized to portions of GC dendrites in the EPL apposed to presynaptic glutamatergic synapses from mitral/tufted cell lateral dendrites (van den Pol, 1995). This suggests that mGluR5 may mediate, at least in part, responses of GCs to glutamatergic inputs from mitral/tufted cells. GCs also express low-to-moderate levels of mGluR2 (Group II) (Ohishi et al., 1993a, 1998), and low levels of mGluR4 and mGluR7 (Group III) (Kinzie et al., 1995; Ohishi et al., 1995; Saugstad

Figure 6-8
The distribution of Group I, Group II, and Group III mGluRs in the MOB. See ***Section 3.8.2*** **for details**



et al., 1997; Wada et al., 1998). The precise cellular localization of these Group II/III mGluRs on GCs is not known. Recent experiments have shown that activation of mGluR5 directly and potently activates GCs. This action is mediated by an apparent inward current that involves, at least in part, a closure of K^+ channels (Heinbockel and Ennis, 2003).

3.8.3 GABA Receptors

$GABA_A$ receptors are present in every layer of MOB except for the IPL (Palacios et al., 1981b; Bowery et al., 1987; Richards et al., 1987; Chu et al., 1990; Zhang et al., 1991; Persohn et al., 1992; Fritschy et al., 1992; Laurie et al., 1992). PG cells moderately express mRNAs for the $\beta 2$ and $\beta 3$ $GABA_A$ receptor subunits (Laurie et al., 1992), and several ET cell subpopulations occur, which are differentially immunoreactive for the $\alpha 1$, $\alpha 3$, or both $\alpha 1$ and $\alpha 3$ receptor subunits (Panzanelli et al., 2005). Putative SA cells of the GCL express $\alpha 1$ and $\beta 2$ receptor subunits (Laurie et al., 1992). At the granule-to-mitral/tufted cell synapses of the EPL, $\alpha 1$, $\beta 2$, $\beta 3$, and $\gamma 2$ $GABA_A$ receptor subunits occur (Fritschy et al., 1992; Giustetto et al., 1998; Sassoè-Pognetto et al., 2000). Mitral/tufted cells also express β_1 $GABA_A$ receptor subunits (Laurie et al., 1992). In addition,

some mitral cells, middle tufted cells, and deep tufted cells express the $\alpha 3$ $GABA_A$ receptor subunit, and many of the mitral cells coexpress CR (Panzanelli et al., 2005). The $\alpha 1$ $GABA_A$ receptor subunits are perisynaptic, which suggests that GABA overflow from nearby synapses might regulate glutamate release from mitral/tufted cell dendrites (Panzanelli et al., 2004). GCs also express $GABA_A$ receptors, including the $\alpha 2$, $\alpha 4$, $\alpha 5$, $\beta 3$, and δ receptor subunits (Laurie et al., 1992) and they exhibit inhibition (Mori and Kishi, 1982), which in a lower vertebrate (tiger salamander) has been shown to be GABAergic (Wellis and Kauer, 1994). In $GABA_A$ $\beta 3$ receptor subunit-deficient mice, functional expression of GC $GABA_A$ receptors was almost eliminated, amplitudes of mitral/tufted cell miniature IPSPs, theta-frequency oscillations, and γ-frequency oscillations were increased, and discrimination of closely related mixtures of alcohols after training was poor relative to normal mice (Nusser et al., 2001). These results provide functional evidence for the importance of both GC and mitral/tufted cell $GABA_A$ receptors in olfaction.

$GABA_B$ receptors are restricted to the GL in MOB (Bowery et al., 1987; Chu et al., 1990). However, there are reports that $GABA_B$ autoreceptors modulate GABA release at granule-to-mitral cell reciprocal synapses (Isaacson and Vitten, 2003). Activation of $GABA_B$ receptors has been observed to reduce dendrodendritic inhibition via suppression of GABA release from GCs due to reduction of high voltage-activated Ca^{2+} currents (Isaacson and Vitten, 2003). In a lower vertebrate (frog), $GABA_B$ and dopamine D_2 receptors both appear to strengthen mitral/tufted cell odor signaling by reducing spontaneous activity (Duchamp-Viret et al., 2000).

3.8.4 Glycine and Glycine Receptors

Cells in the EPL and GCs are also immunoreactive for glycine (Pourcho et al., 1992), and the MOB contains significant levels of both this amino acid and taurine, which inhibit cultured olfactory bulb cells (Trombley and Shepherd, 1994; Trombley et al., 1999) and mitral/tufted cells in situ (Belluzzi et al., 2004). The MOB exhibits strong labeling for glycine receptors (van den Pol and Gorcs, 1988), and the β receptor subunit has been localized to mitral/tufted cell synapses (Malioso et al., 1991).

3.8.5 Gap Junctions

Gap junctions are thought to play a role in synchronization of MOB activity (Schoppa and Westbrook, 2002; Christie et al., 2005; Hayar et al., 2005). Gap junction inhibitors block γ-frequency (20–70) Hz oscillations generated by chemically and electrically coupled networks of mitral and GCs (Friedman and Strowbridge, 2003), suggesting a role for both types of synapses. *Table 6-3* summarizes the distribution of gap junctions and the gap junction proteins, connexins, in the MOB. Gap junctions have been observed on mitral, tufted, and GC bodies (Reyher et al., 1991; Paternostro et al., 1995; Miragall et al., 1996; Kosaka and Kosaka, 2003). In the GL, mitral/tufted cell dendrites have also been observed to form gap junctions with each other, with PG cells, and with processes of unidentified cells (Kosaka and Kosaka, 2003, 2004, 2005; Kosaka et al., 2005; Rash et al., 2005). The junctions tend to occur as mixed synapses with glutamatergic synapses. Some of the unidentified processes involved in these synapses are not immunoreactive for either DA or GABA and could be mitral/tufted cell dendrites (Kosaka and Kosaka, 2003). In support of this, mitral/tufted cell dendrites of a lower vertebrate (tiger salamander) have been observed to form asymmetrical synapses with each other in the GL (Allen and Hamilton, 2000). In addition to their GL synapses, mammalian mitral/tufted cell dendrites form some gap junctions with dendrites of GCs (Landis et al., 1974; Kosaka et al., 2005) and other interneurons (Kosaka and Kosaka, 2003) in the EPL.

The predominant gap junction protein of MOB neurons appears to be connexin36 (Condorelli et al., 1998, 2000; Belluardo et al., 2000; Rash et al., 2000, 2005), although mitral/tufted cells and unidentified interneurons in the EPL and GCL have been reported to express other connexin mRNAs (connexin43, Miragall et al., 1996; connexin45, Zhang and Restrepo, 2002) or proteins (connexin43, Theis et al., 2003) that are mainly expressed by glial cells. It is noteworthy that expression of connexin36 mRNA is particularly high within (but not uniform among) the glomeruli (Teubner et al., 2000; Zhang and Restrepo, 2003), and

that expression of this connexin remains high into adulthood (Hormuzdi et al., 2001). This is in contrast to the hippocampus, where connexin36 mRNA expression peaks during early postnatal life and subsequently declines (Rozental et al., 2000). In addition, γ-frequency electrical signaling is disrupted in connexin36 knockout mice (Hormuzdi et al., 2001), providing evidence that this connexin is involved in oscillatory signaling. Gap junction channels formed by connexin36 exhibit unitary conductances of ~15 pS, weak transjunctional voltage dependence, and are also permeable to cAMP and IP_3 (Rozental et al., 2000; Teubner et al., 2000). Thus, gap junctions connecting MOB neurons could participate in both fast oscillatory signaling and slower, second messenger-mediated signaling, even in adults.

3.9 Neuromodulatory Inputs to MOB

MOB and most components of POC receive extrinsic inputs from cholinergic, noradrenergic, serotonergic, and dopaminergic cell groups in the brainstem and basal forebrain.

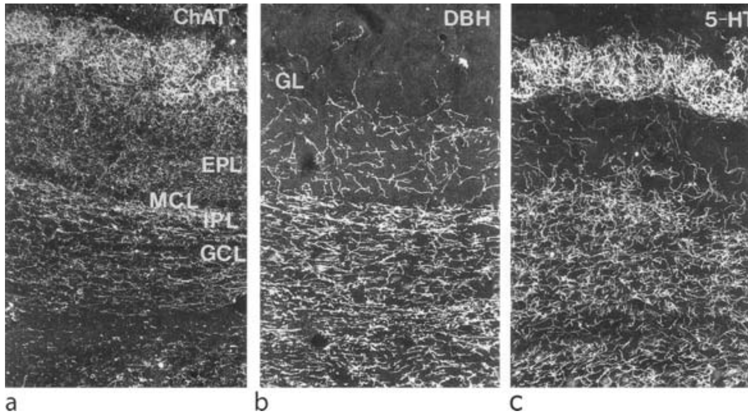
3.9.1 Cholinergic Inputs to MOB

3.9.1.1 Cholinergic Innervation Pattern and Receptor Distribution In the mouse, about 3.5% of all neurons that project to the bulb originate in the nucleus of the horizontal limb of the diagonal band (NDB); far fewer originate in the vertical limb of DB (Carson, 1984; Shipley and Adamek, 1984). At least two distinct transmitter-specific populations of NDB neurons project to the MOB (Zaborszky et al., 1986). About 20% of the NDB neurons that project to the bulb are cholinergic; most of these cells are concentrated in the rostromedial portion of the horizontal limb of NDB. Many NDB-MOB projection neurons are GABAergic and occur mainly in the caudo-lateral aspect of NDB (Zaborszky et al., 1986). AChE is concentrated in the IPL, GCL, inner third of the EPL, and the GL. Some glomeruli are more intensely stained for AChE and correspond to regions of leutenizing hormone releasing hormone (LHRH) innervation (Zheng et al., 1988), and may include the modified glomerular complex as defined by Greer and colleagues (Teicher et al., 1980; Greer et al., 1982). There are also AChE-positive neurons in the bulb (Nickell and Shipley, 1988b). Choline acetyltransferase (ChAT), the biosynthetic enzyme for ACh, is located in axons distributed in the same layers as described for AChE. As shown in *Figure 6-9*, cholinergic fibers are distributed throughout the MOB, but are especially heavy in the GL and IPL. The GABAergic projection from NDB (Zaborszky et al., 1986) is more difficult to characterize than the cholinergic projection, because the intrinsic GABAergic PG cells and GCs provide intrinsic GABAergic innervation.

Cholinergic receptor localization in the MOB is in close agreement with terminal staining from the NDB (*Table 6-4*). Muscarinic receptors are found in all layers while nicotinic receptors are found in all layers except the IPL (see *Table 6-4*). The EPL exhibits intense staining for muscarinic-1 (M_1), M_3, and M_4 receptors (Rotter et al., 1979; Spencer et al., 1986; Buckley et al., 1988; Fonseca et al., 1991b). M_2 receptors are immunocytochemically localized to PG cells in the GL and tufted cells in the EPL (Fonseca et al., 1991a). M_2 receptors are also present in the IPL and GCL. Nicotinic receptors show a different regional distribution throughout the MOB and are concentrated in the GL and EPL (Hunt and Schmidt, 1978; Sahin et al., 1992).

3.9.1.2 Cholinergic Actions in MOB Only limited information is available about cholinergic actions in MOB. Electrical activation of NDB has been reported to depress (Nickell and Shipley, 1988a) or increase (Kunze et al., 1991, 1992) mitral cell activity indirectly via primary effects on GABAergic GCs. NDB stimulation also reduced the field potential in the MOB caused by stimulation of the anterior commissure (Nickell and Shipley, 1993), an effect mediated by presynaptic inhibition of anterior commissure terminals via muscarinic receptors. One interpretation of these results is that cholinergic input to MOB may function to modulate interhemispheric transmission of olfactory information. In this regard, it is noteworthy that anterior commissural fibers are required for access and recall of olfactory memories between the two hemispheres. Infusion of ACh into MOB was reported to reduce paired-pulse depression of lateral olfactory tract (LOT)-evoked field potentials recorded in the GCL. This effect was attributed to

Figure 6-9
Neuromodulatory transmitter inputs to MOB. Darkfield photomicrographs showing the distribution of cholinergic (a), noradrenergic (b), and serotonergic (c) fibers revealed respectively with immunohistochemistry for choline acetyltransferase (ChAT), dopamine-β-hydroxylase (DBH), and serotonin (5-HT). Reprinted from Handbook of Chem. Neuroanat. Integrated Sys. CNS, Vol. 12, Part III, Chapter III, The Olfactory System, M. Shipley et al., pp. 469–573, 1996, with permission from Elsevier, Ltd



muscarinic receptor-mediated inhibition of GABA release from GCs (Elaagouby et al., 1991). In slice preparations, nicotinic but not muscarinic receptor agonists directly excited mitral cells, and this effect appeared to be due to an inward current with a reversal potential of –5 to +10 mV (Castillo et al., 1999). In slices, muscarinic receptor agonists inhibited GCs (Castillo et al., 1999), and paradoxically, also appeared to increase GABA release from these cells. The same study reported that in the GL only bipolar PG cells were sensitive to nicotine (Castillo et al., 1999). The morphological identity of these cells is unclear.

3.9.2 Dopaminergic (DA) Input to MOB

There is no known extrinsic DA innervation of the MOB. As noted earlier, however, the MOB contains several hundred thousand intrinsic JG DA neurons that mediate potent presynaptic inhibition of ON terminals via activation of D2 receptors. This presynaptic inhibition as well as DA receptor localization is discussed in *Section 3.2.3.2*.

3.9.3 Noradrenergic (NE) Input to MOB

3.9.3.1 NE Innervation Pattern and Receptor Distribution A significant modulatory input to the MOB is from the pontine nucleus, locus coeruleus (LC). In the rat, all LC neurons contain the neurotransmitter, norepinephrine (NE); LC contains the largest population of NE neurons in the brain. It has been estimated that up to 40% of LC neurons (400–600 of a total of 1,600 LC neurons) project to the bulb in the rat (Shipley et al., 1985). A subset of LC neurons projecting to MOB contain NPY (Bouna et al., 1994). NE fibers terminate in MOB with laminar specificity. LC axons project mainly to the subglomerular layers of the bulb, particularly the IPL and GCL (McLean et al., 1989). The EPL and MCL are moderately innervated, whereas the GL is nearly devoid of NE input.

NE receptors occur in multiple layers of the MOB and they are expressed by multiple cell types, in general consistent with the pattern of NE fiber innervation (*Figure 6-10* and *Table 6-4*). Receptor

Figure 6-10
The distribution of NE receptors in the MOB. See *Section 3.9.3* **for details. CFF, centrifugal fibers**

localization studies also suggest that individual MOB cells express multiple NE receptor subtypes. α receptors are abundantly expressed in MOB. Binding sites for $\alpha 1$ receptors are particularly dense in the EPL, and moderate in the MCL and IPL/GCL (Young and Kuhar 1980a; Sargent-Jones et al., 1985); the density of $\alpha 1$ receptors in the EPL was the highest in the brain (Young and Kuhar, 1980a). Consistent with these findings are observations that $\alpha 1$ receptor mRNA is expressed by mitral cells ($\alpha 1_A$, $\alpha 1_B$, $\alpha 1_D$ subtypes) and GCs ($\alpha 1_A$, $\alpha 1_D$ subtypes) (McCune et al., 1993; Pieribone et al., 1994; Domyancic and Morilak, 1997; Day et al., 1997). The MCL, IPL, and GCL express moderate-to-dense levels of $\alpha 2$ receptors (Young and Kuhar, 1979; Nicholas et al., 1993; Rosin et al., 1996; Talley et al., 1996; Winzer-Serhan et al., 1997a, b), and $\alpha 2_C$ receptor mRNA is expressed by both mitral cells and GCs (Nicholas et al., 1993; Rosin et al., 1996; Winzer-Serhan et al., 1997a, b). The high density of $\alpha 2$ receptor binding sites and NE fibers in the IPL/GCL suggests the possibility that these receptors may be present presynaptically on axon terminals of NE fibers themselves or on other centrifugal inputs to the soma and/or proximal dendrites of GCs (*Figure 6-10*). Unidentified JG neurons have been reported to express $\alpha 1$ and $\alpha 2$ receptors (Rosin et al., 1996; Winzer-Serhan et al., 1997a, b). By contrast, the level of β receptors is relatively low in the MOB, and they appear to

be localized preferentially to the GL, IPL, and GCL (Palacios and Kuhar, 1982; Booze et al., 1989; Wanaka et al., 1989; Woo and Leon, 1995). JG, mitral, and tufted cells, as well as subsets of GCs express the $\beta 1$ receptor subtype (Yuan et al., 2003).

3.9.3.2 Physiological Actions of NE Although, NE clearly plays significant roles in olfactory function, the effects of NE at the cellular and network levels are somewhat discrepant. For example, LC stimulation was reported to have no effect on LOT-evoked field-potentials recorded in the GCL (Perez et al., 1987). A subsequent study reported that LC stimulation initially decreased and then subsequently increased paired-pulse depression of GC field-potential responses to LOT stimulation (Okutani et al., 1998). These effects were attributed to activation of β receptors. Another field-potential study reported that NE infusion into MOB, acting at $\alpha 1$ receptors, increased the depolarization of GC dendrites elicited by LOT stimulation. Mitral cell responses to antidromic shocks were not affected, suggesting that NE excites GC (Mouly et al., 1995). In neonatal animals, β receptor stimulation in MOB decreased LOT-evoked, paired-pulse inhibition of GC field potentials (Wilson and Leon, 1988). It is unclear if this was mediated by presynaptic inhibition of transmitter release from MCs and/or increased excitability of GCs.

Cellular recording studies are also somewhat discrepant. In the rabbit and cat, Salmoiraghi et al. (1964) and McLennan (1971) found that iontophoretically applied NE inhibited mitral cells. This effect was blocked by the $GABA_A$ receptor antagonist, bicuculline. In the isolated turtle bulb (Jahr and Nicoll, 1982), mitral cell spike activity increased, and GABAergic IPSPS decreased, following bath application of NE. In dissociated MOB cultures, NE decreased mitral cell-to-GC dendrodendritic synaptic transmission acting presynaptically at $\alpha 2$ receptors to decrease Ca^{2+} currents in both granule and mitral cells (Trombley, 1992; Trombley and Shepherd, 1992). NE release, evoked by selective chemical activation of LC in vivo, enhanced the response of mitral cells in response to weak (i.e., perithreshold) but not strong (i.e., suprathreshold) stimulation of the olfactory epithelium (Jiang et al., 1996). Interestingly, NE release from LC axon terminals is facilitated and suppressed by activation of presynaptic nicotinic and muscarinic cholinergic receptors, respectively (El-Etri et al., 1999). In rat MOB slices, application of NE or $\alpha 1$ receptor agonists, but not $\alpha 2$ or β receptor agonists, also selectively increased mitral cell responses to perithreshold intensity ON stimulation (Ciombor et al., 1999). Noradrenergic agonists had no effect on ON-evoked field-potentials recorded in the GL, or on ON-evoked postsynaptic currents in mitral cells (Hayar et al., 2001). This suggests that NE-evoked modulation of ON-evoked mitral cell spiking is mediated by postsynaptic actions on bulb neurons. In voltage clamp recordings, NE or $\alpha 1$ agonists directly evoked an inward current in mitral cells that appeared to be due to closure of K^+ channels. In current clamp recordings from bistable mitral cells, $\alpha 1$ agonists shifted the membrane potential from the downstate (–52 mV) toward the upstate (–40 mV), and significantly increased spike generation in response to perithreshold ON input. Taken together, these findings suggest that NE release directly alters mitral cell excitability in a manner that could increase their sensitivity to weak ON input, perhaps to improve the detection of weak odorants.

NE inputs to the bulb are critical to olfactory function. Olfactory cues increase the discharge of LC neurons in behaving animals (Aston-Jones and Bloom, 1981) and increase NE levels in the MOB (Chanse and Kopin, 1968; Rosser and Keverne, 1985; Brennan et al., 1990). LC projections to the main and accessory olfactory bulb are pivotal to the formation and/or recall of specific olfactory memories, pheromonal regulation of pregnancy and postpartum maternal behavior (Pissonnier et al., 1985; Kaba and Keverne, 1988; Brennan et al., 1990; Kendrick et al., 1992). NE plays an important role in the so-called Bruce effect in mice: when impregnated female mice are exposed to the odor of a strange male, they abort; if exposed to the odor of the impregnating male they do not abort (Kaba et al., 1989). Systemic administration of adrenergic receptor antagonists or 6-OHDA lesions, selectively destroying only the NE inputs to the MOB, cause the female to abort when presented with the odor of the impregnating male (Rosser and Keverne, 1985; Kaba and Keverne, 1988; Brennan et al., 1990). Finally, NE has been shown to play a critical role in olfactory learning in young animals. In neonatal rats, NE release via tactile stimulation leads to a preference for an odor associatively paired with this stimulation (Sullivan et al., 1989). The conditioned preference is associated with odor-specific metabolic changes in the bulb (Coopersmith and Leon, 1984). Following the conditioning, there is an increased inhibition of mitral cells by the odor (Sullivan et al., 1989). Such

conditioning is abolished by eliminating NE input to the bulb or via β receptor antagonists (Sullivan et al., 1989, 1992, 2000; Wilson and Sullivan, 1991; Moriceau and Sullivan, 2004). Recent studies from McLean's laboratory demonstrate that this β receptor-dependent neonatal learning involves activation of intracellular cAMP and CREB pathways (see McLean and Harley, 2004 for review).

3.9.4 Serotonergic (5-HT) Inputs to MOB

3.9.4.1 5-HT Innervation Pattern, Receptor Distribution, and Physiological Actions The midbrain dorsal and median raphe provides strong inputs to the MOB. In the rat, about 1,000 dorsal and 300 median raphe neurons project to the bulb. These neurons are serotonergic and they do not contain TH (McLean and Shipley, 1987a, b) or substance P (Zaborszky et al., 1986). As shown in *Figure 6-9*, 5-HT fibers are present in all layers of MOB, but with varying densities. Input to the GL is especially dense, while the EPL contains very low density. [^{3}H]5-HT-labeled boutons have been observed in close proximity to probable SA cells in the EPL (Halász et al., 1978). The MCL, IPL, and GCL have a fairly heavy and uniform innervation, but not as dense as that of the GL. Thick serotonergic fibers preferentially innervate the glomeruli of MOB, whereas thinner serotonergic axons preferentially innervate inframitral layers (McLean and Shipley, 1987a, b). In neocortex, thick axons arise from the median raphe and thin axons arise from dorsal raphe (McLean and Shipley, 1987a, b) and the same segregation occurs in MOB.

In agreement with the 5-HT fiber distribution, 5-HT receptors are localized in most layers of the MOB (*Table 6-4*). The 5-HT$_{1A}$ subtype is present on processes in the EPL, MCL, and minimally in the GCL; mitral cells and GCs appear to express the 5-HT$_{1A}$ receptor (Pompeiano et al., 1992). 5-HT$_{1C}$ is present in the GCL. It is possible that many of the cells possessing 5-HT receptors are glia (Whitaker-Azmitia et al., 1993). The 5-HT$_2$ receptors are present in the GL, EPL, and MCL. The 5-HT$_{2A}$ receptor subtype is found in the EPL and in mitral and tufted cells (McLean et al., 1993, 1995; McLean, 1994; Pompeiano et al., 1994; Hamada et al., 1998; Cornea-Hebert et al., 1999). In mitral and tufted cells, 5-HT$_{2A}$ receptors colocalize with the β1 receptor (Yuan et al., 2003). The 5-HT$_{2A}$ receptors are also present in unidentified JG cells in the GL (Hamada et al., 1998; Cornea-Hebert et al., 1999). The 5-HT$_{2C}$ receptor subtype is expressed at fairly high levels by GCs and at relatively low levels by unidentified JG neurons (Clemett et al., 2000). JG cells have also been reported to express 5-HT$_3$ receptors (Tecott et al., 1993).

At present, there is only limited data about the actions of serotonin in the MOB. In the GL, it was recently reported that serotonin depolarized 34% of JG cells in vitro via activation of 5HT$_{2C}$ receptors (Hardy et al., 2005). The serotonin-induced depolarization was due to activation of a nonselective cation current with a reversal potential of –44 mV. The heterogeneous electrophysiological properties of 5HT-responsive JG cells suggested that several types of JG cells could be targeted by 5HT centrifugal fibers. A subset of mitral cells was also depolarized by serotonin acting at 5HT$_{2A}$ receptors. In contrast with these results, another subset of mitral cells was hyperpolarized by serotonin, an action that was indirectly mediated by GCs as it was blocked by GABA$_A$ receptor antagonists (Hardy et al., 2005). This effect of serotonin was also thought to be mediated by 5HT$_{2A}$ receptors. Behavioral studies indicated that lesion of serotonergic fibers reversed conditioned olfactory learning (Morizumi et al., 1994), and also induced glomerular atrophy. Behavioral work on neonates by McLean et al. (1996) showed that serotonin depletion or 5-HT$_2$ receptor antagonism compromised olfactory learning and that serotonin release or 5-HT$_2$ receptor activation promoted odor conditioning. 5-HT release appeared to facilitate β receptor-mediated, NE-induced olfactory learning by facilitating cAMP mechanisms (see McLean and Harley, 2004 for review).

4 Olfactory Input Regulates Neurochemistry of Specific MOB Neurons

ORNs turn over throughout life, most MOB interneurons are added after birth, and new interneurons are continually added during adulthood. The MOB is consequently a highly plastic neural system that is readily affected by both sensory experience and deprivation. A variety of studies showed that occlusion of one naris

during early postnatal life markedly affected development of the ipsilateral MOB, resulting in numerous cellular changes and ~25% smaller MOB (Brunjes, 1994). The studies also showed that naris occlusion resulted in reduced DA levels (Baker et al., 1983; Brunjes et al., 1985; Wilson and Wood, 1992). During development, the maturing dopaminergic JG neurons only exhibited TH immunoreactivity after they reached the GL, and they failed to do so after naris occlusion (McLean and Shipley, 1988; Baker, 1990; Baker and Farbman, 1993; Baker et al., 1993). In adults, both naris occlusion and destruction of the mature olfactory sensory neurons by nasal irrigation with $ZnSO_4$ or detergent, or by severing the ON, reduced transneuronal regulation of DA levels and TH expression in rats (Nadi et al., 1981; Kawano and Margolis, 1982; Baker et al., 1983, 1993; Erlich et al., 1990; Cho et al., 1996; Couper Leo et al., 2000), hamsters (Kream et al., 1984) and dogs (Nadi et al., 1981). In concert with the reduced TH expression, dopamine D2 receptor density was increased in the ONL and GL (Guthrie et al., 1991). TH expression was also downregulated in mice homozygous for a null mutation in the olfactory cyclic nucleotide gated channel subunit-1 (OCNC1), which rendered them functionally anosmic (Baker et al., 1999). The loss of TH expression following naris occlusion and deafferentation was not due to cell death, because JG neurons could be detected with antibodies to other DA enzymes (Baker et al., 1984). Moreover, both GAD and GABA, which are coexpressed by many dopaminergic JG neurons, were still detected (Kosaka et al., 1987a, b, c; Baker et al., 1988, 1993; Stone et al., 1990). Depolarizing stimuli could induce TH expression in vitro and in vivo (McMillian et al., 1994; Philpot et al., 1998), and the in vitro studies showed that the induction required Ca^{2+} influx into the bulb neurons (Cigola et al., 1998). In an MOB neuron/olfactory epithelium coculture, TH expression was abolished by NMDA receptor blockade (Puche and Shipley, 1999), suggesting that glutamate released by ORNs stimulates the dopaminergic JG neurons, resulting in Ca^{2+} influx and regulation of TH expression. Thus, both the developmental induction and maintenance of the DA phenotype appear to be transneuronally regulated and to depend on the presence and normal functioning of the ON. Although the intracellular mechanisms remain to be elucidated, the distributions of c-fos immediate early gene mRNA and Fos protein immunoreactivity were found partially to overlap with TH distribution and were downregulated following naris occlusion (Guthrie and Gall, 1995a, b; Jin et al., 1996). Fos-B was implicated in the regulation of TH expression through interactions with the AP-1 motif (Liu et al., 1999).

The expression of other neurotransmitters and receptors is also influenced by the afferent sensory input to the MOB. In the hamster, many JG neurons express substance P, and this peptide was found to be downregulated following chemical deafferentation (Kream et al., 1984). By contrast in rats, glomerular mGluR1 immunoreactivity was increased. Initially, the mGluR1a mRNA level increased, but it then declined (like TH expression), presumably due to product inhibition (Ferraris et al., 1997; Casabona et al., 1998). As with chemical deafferentation, neonatal naris occlusion of rats and mice had both negative and positive effects. It reduced the density of β1- and β2-adrenergic receptors as determined by quantitative autoradiography (Woo and Leon, 1995), although NE levels were not reduced following either naris occlusion (Brunjes et al., 1985) or chemical deafferentation (Nadi et al., 1981). Similarly, although levels of GluR1 were not reduced following chemical deafferentation (Ferraris et al., 1997), immunoreactivity of cell bodies in the EPL for both GluR1 (Hamilton and Coppola, 2003) and for PV were greatly reduced, as was immunoreactivity of nondopaminergic JG neurons for calbindin (Philpot et al., 1997). Focal surgical deafferentation had similar effects on PV and calbindin immunoreactivity (Couper Leo et al., 2000). CR immunoreactivity of other interneurons was not affected, however. In addition, although the number of synapses between mitral cell bodies and GC dendrites were reduced following naris occlusion, mitral/tufted cell inhibition appeared to be increased, possibly via enhanced NMDA receptor-mediated excitation of the GCs by the mitral/tufted cells at their reciprocal synapses (Wilson, 1995). Expression of voltage-sensitive Na^{+} channel αII and β1 subunits was also downregulated in tufted cells, but not in mitral cells (Sashihara et al., 1997). The afferent sensory input to MOB therefore appears to influence the expression of a variety of neurotransmitters, receptors, and ion channel proteins, with different effects observed on different cell types.

Neurotrophic factors, receptors, and kinases were also shown to be affected by naris occlusion. These include insulin receptor (IR) kinase, brain-derived neurotrophic factor (BDNF), neurotrophin receptors TrkB and TrkC, and mitogen-activated protein kinase/extracellular signal-related kinase (MAPK/ERK)

(Mackay-Sim and Chuah, 2000). Expression of IR kinase was reduced, as was the insulin-induced suppression of current through the Kv1.3 channel, which is typically tyrosine phosphorylated in the N and C termini by IR kinase (Fadool et al., 2000). The Kv1.3 channel carries most of the outward current of cultured MOB neurons (Fadool and Levitan, 1998). Moreover, BDNF levels initially increased in vivo and subsequently decreased, without concomitant effects on TrkB levels (McLean et al., 2001; Tucker and Fadool, 2002). In cultured MOB neurons isolated from the occluded side, however, the BDNF-induced phosphorylation of Kv1.3 was increased, indicating that tyrosine kinase activity was increased. Activation of ERK pathway was also downregulated (Mirich et al., 2004). Levels of other kinases did not appear to be altered, however, at least as examined by immunocytochemical staining (Liu, 2000). These results suggest that altered levels of neurotrophic factors and altered kinase expression or activity may contribute to the developmental changes observed in MOB neurons following naris occlusion.

5 Primary Olfactory Cortex: Piriform Cortex

The MOB projects to a collection of structures referred to as POC (de Olmos et al., 1978). These structures may be divided into three groups: (1) the AON, (2) medial olfactory cortex (indusium griseum, anterior hippocampal continuation, taenia tecta, and the olfactory tubercle), and (3) lateral olfactory cortex comprising, from rostral to caudal, PC and the periamygdaloid, transitional and entorhinal cortices (*Figure 6-7*). At least from an olfactory perspective PC is perhaps the most extensively studied and well understood member of POC. A thorough presentation of the cytoarchitecture, connections, and neurochemistry of each of the components of POC is beyond the scope of the present report, and readers are directed to more complete reviews of these subjects (Shipley et al., 1996, 2004). Here, we focus on PC (*Figures 6-3* and *6-7*) as an example of POC.

5.1 Organization and Architecture

PC is the largest component of the lateral olfactory cortical areas. It extends rostrocaudally and is located in the cortical mantle ventral to the rhinal sulcus (*Figure 6-3*). Haberly and Price (1978a) divided PC into three layers that were further subdivided on the basis of cytoarchitecture and afferent connections. Layer I, the superficial plexiform layer, is divided into Ia and Ib, which receive different afferents: layer Ia, from the ipsilateral MOB, and layer Ib, association fibers from AON and from other parts of POC. Layer II, the superficial compact cell layer, is divided into two zones; the more superficial zone has a lower cell density and the deeper zone has a higher cell density. Layer III is the thickest cell layer. The endopiriform nucleus lies deep to the PC (Loo, 1931; Haberly and Price, 1978a). Behan and Haberly (1999) reported that this nucleus, while similar in many regards to PC proper, has unique intrinsic and extrinsic connections that differ from PC. Additionally, electrophysiological properties of endopiriform neurons, such as certain K^+ currents (e.g., A-current), differ from those of PC neurons (Banks et al., 1996). As reviewed later, there is considerable rostrocaudal heterogeneity in the structure and connections of anterior versus posterior PC (Haberly and Price, 1978a; Luskin and Price, 1983). There is evidence for distinct subdivisions within the anterior PC based on cytoarchitecture, connections, and neurochemistry (Ekstrand et al., 2001b). Candidate transmitters and neurotransmitter receptors in PC are summarized in *Tables 6-5* and *6-6*.

5.2 PC Cell Types

Neurons in PC can be divided into two main classes: (1) principal or output neurons—the pyramidal cells and (2) intrinsic interneurons.

Table 6-5
Neuroactive substances in PC neurons

Neurotramitter	Cell Location	Cell Type	References
Calbindin/ Calretinin	Mainly layer II	Pyramidal, basket, bi-multipolar	Celio (1990), Morales and Bloom (1997)
CCK	Mainly layer II and III	Pyramidal, multipolar, basket	Roberts et al. (1982), Westenbroek et al. (1987)
Dyn B	Layer II and III	Nonpyramidal fusiform, multipolar	Fallon and Leslie (1986)
ENK	Mainly layer II	Fusiform, pyramidal, multipolar	Harlan et al. (1987)
GABA/GAD	All layers	Diverse interneurons	Ekstrand et al. (2001a), Haberly et al. (1987), Morales and Bloom (1997)
Glutamate	Layers II and III	Pyramidal cells	See *Section 3.8.1*
Neurotensin	NR	NR	Hara et al. (1982)
Parvalbumin	Mainly layers II and III	Multipolar, basket	Celio (1990)
VIP	Mainly layers II and III	Bipolar, basket	Ekstrand et al. (2001a), Roberts et al. (1982), Sanides-Kohlrausch and Wahle (1990b)

NR, not reported. Adapted from Handbook of Chem. Neuroanat. Integrated Sys. CNS, Vol. 12, Part III, Chapter III, The Olfactory System, M. Shipley et al., pp. 469–573, 1996, Elsevier, Ltd

5.2.1 Pyramidal Cells

PC has two principal layers of pyramidal cells, layers II and III, corresponding to superficial and deep pyramidal cells. Both superficial and deep pyramidal neurons share characteristic features similar to pyramidal cells in the hippocampus and other cortical areas, including: (1) a primary apical-dendritic trunk that extends radially toward the pial surface and arborizes in layer Ia and Ib (Haberly, 1983), (2) secondary or basal dendrites that extend from the soma into deeper parts of PC. Both the apical and basal dendrites are heavily invested with spines and varicosities, and (3) a myelinated axon that typically extends deep to the soma that terminates on other local pyramidal cells and interneurons (see later), or projects back to MOB. Reconstructions of intracellularly filled pyramidal cells show that they have extensive axonal projections covering almost an entire cerebral hemisphere, including local connections to anterior and posterior PC as well as arborizations in orbital cortex, insular cortex, olfactory tubercle, perirhinal cortex, entorhinal cortex, and amygdaloid cortex (Johnson et al., 2000). The collaterals of deep pyramidal axons travel into the endopiriform nucleus (Tseng and Haberly, 1989), whereas those of superficial pyramidal neurons do not appear to enter this structure. The apical dendritic tree of superficial pyramidal cells generally branches more extensively and is more densely invested with spines and varicosities than that of deep pyramidal cells. Pyramidal cells contain glutamate and participate in intrinsic (intra-PC) and extrinsic excitatory projections as discussed later.

5.2.2 Interneurons

PC possesses a variety of interneurons as evidenced by morphological and neurochemical heterogeneity (Haberly and Presto, 1986; Haberly et al., 1987; Ekstrand et al., 2001a). A thorough consideration of PC

Table 6-6
Neurotransmitter receptors in the PC

Receptor	Layer	References
Cholinergic		Buckley et al. (1988), Hill et al. (1993), Levey et al. (1991), Rotter et al. (1979), Sahin et al. (1992), Seguela et al. (1993), Spencer et al. (1986)
mAChR1	I, II	
mAChR2	II	
mAChR3	II	
mAChR4	II	
nAChR	II, III	
Noradrenergic		Day et al. (1997), Domyancic and Morilak (1997), Nicholas et al. (1993), Palacios and Kuhar (1980), Pieribone et al. (1994), Rosin et al. (1996), Sargent-Jones et al. (1985), Talley et al. (1996), Unnerstall et al. (1984), Wanaka et al. (1989), Winzer-Serhan et al. (1997a, b), Young and Kuhar (1979, 1980a)
$\alpha1$	II, III	
$\alpha2$	I, II, III	
$\beta1$	II	
$\beta2$	II	
Dopaminergic		Fremeau et al. (1991), Huang et al. (1992), Mansour et al. (1990a, b)
D_1	II	
D_2	NR	
Serotonergic		Clemett et al. (2000), Cornea-Hebert et al. (1999), Hamada et al. (1998), Hoffman and Mezey (1989), Mengod et al. (1990a, b), Morales and Bloom (1997), Pompeiano et al. (1992, 1994), Tecott et al. (1993), Wright et al. (1995)
5-HT_{1A}	II	
5-HT_{1C}	II	
$5\text{-HT}_{2A/C}$	I, II, III	
5-HT_3	NR	
Glutamatergic		Gall et al. (1990), Kinoshita et al. (1998), Kinzie et al. (1995), Monaghan et al. (1985), Ohishi et al. (1993a, b, 1995, 1998), Petralia and Wenthold (1992), Petralia et al. (1994a, b), Romano et al. (1995), Saugstad et al. (1997), Shigemoto et al. (1992), Sun et al. (2000), Wada et al. (1998), Wisden and Seeburg (1993)
KA	II	
NMDA	Ia, II	
AMPA	II	
mGluR		
Group I mGluR (mGluR1/5)	II, III	
Group II mGluR (mGluR2,3)	NR	
Group III mGluR (mGluR4,7,8)	Ia	
GABAergic		Bowery et al. (1987), Margeta-Mitrovic et al. (1999), Palacios et al. (1981b), Young and Kuhar (1980b)
$GABA_A$	I, III	
$GABA_B$		

NR, not reported

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interneurons is beyond the scope of this review and detailed descriptions of these cells are available elsewhere (Shipley et al., 1996). Here, we present the distribution of the main interneuron types and some of their major neurochemical features. Interneurons are distributed throughout all layers and regions of this structure, and most, if not all, contain GABA (Haberly et al., 1987). Major interneuronal subtypes include the following:

1. Horizontal cells with large fusiform somata, found only in the superficial part of layer I (Haberly, 1983). These GABAergic cells produce dendrites that ramify within layer Ia and to a lesser extent within layer Ib (Haberly et al., 1987). Layer I interneurons are thought to function in feedforward inhibitory systems.
2. Spiny cells, found in layers I and III. Spiny actually refers to several distinct morphological subtypes (e.g., those with spherical or fusiform somata) that exhibit dendritic spines (Haberly, 1983). The dendrites of layer I cells extend into all parts of layer I and occasionally into deeper layers. Spiny cells give rise to unmyelinated axons that are horizontally oriented. Giant cells, another subcategory of spiny cell, have the largest soma size in PC. These cells are concentrated in the ventral parts of layer III.
3. Smooth cells, also found in layers I and III. Those in layer I exhibit a variety of cell shapes and sizes and they are distinguished by a lack of spines on the cell body or dendrites and by the presence of beaded varicosities on the distal dendrites. Smooth cells are the most numerous nonpyramidal cells in layer III, and they are preferentially distributed in the middle and deep parts of layer III. The dendrites emerge from numerous sites on the soma, usually branch once or twice near the soma, and then extend radially in all directions, with few subsequent bifurcations. The dendritic tree typically respects the boundaries of layer III.
4. Neurogliaform cells, found in layers I and II, have spherical somata and they are the most common cell type in layer I. The dendritic trees of these cells are usually restricted to a single sublamina in layer I. The axons are unmyelinated and branch extensively. Neurogliaform cells in layer II are essentially similar to those in layer I.
5. Semilunar cells, located in layer IIa, lack a basal dendritic tree, but they have several apical dendrites that arborize in layer I and axons that extend deep to the somata.
6. Multipolar cells, located throughout layer III and the endopiriform nucleus (Tseng and Haberly, 1989), have dendrites that are confined to layer III. The axons of these cells collateralize and synapse extensively within layer III and also extend to layer I. Many multipolar cells are GABAergic (Haberly et al., 1987).

In parallel with their diverse anatomical makeup, interneurons in PC are neurochemically heterogeneous, and they are thought to subserve multiple functions. CR and CCK also colocalize in GABAergic interneurons in PC (Morales and Bloom, 1997). Many GABAergic interneurons, described as "basket cells," colocalize with Ca^{2+} binding proteins (PV, calbindin), VIP, or CCK (Kubota and Jones, 1993; Ekstrand et al., 2001a). Basket cells are primarily distributed in layers II/III and exhibit diverse molecular markers and morphological characteristics. These cells are thought to predominantly form axo-somatic or proximal axo-dendritic synapses with neurons in layers II and III, and to participate both in feedback and feedforward inhibitory circuits.

5.3 PC Circuitry

5.3.1 Input from MOB

The output of MOB is through mitral cells and tufted cells. Their main axons gather at the caudo-lateral extent of MOB forming the LOT. These caudally directed axons give off collaterals in the AON and in other regions of POC (*Figure 6-7*). The MOB sends a projection to the entire extent of PC, terminating in the superficial half of layer I, which is layer Ia. Within layer Ia, mitral/tufted cell axons synapse on the apical dendrites of pyramidal cells and with certain types of interneurons (Haberly, 1983). At the ultrastructural

level, mitral/tufted cell axon terminals form asymmetrical synapses with dendritic spines. Some of the outputs of the MOB have a modest degree of topographical organization. For example, neurons in the dorsolateral quadrant of MOB project to the dorsal part of the external subdivision of AON, whereas output cells of the ventral half of MOB project to the lateral subdivision (Schoenfeld and Macrides, 1984). Intracellular HRP injections into mitral cells show that their axons form collateral terminal arbors within AON and PC (Ojima et al., 1984). The terminal arbors have a patchy anterior–posterior distribution in layer Ia of AON and PC in rabbit (Ojima et al., 1984). Some mitral cells branch and project to both PC and the olfactory tubercle. Mitral cells that are close together are reported to have similar patterns of axonal projections to the olfactory cortex (Buonviso et al., 1991). These findings, as well as observation that ORNs bearing the same odor receptor converge on single glomeruli, suggested that mitral cells of the same glomerulus might terminate with topographic specificity in PC. Studies by Buck and colleagues (Zou et al., 2001), using a genetic transneuronal tract tracing approach, reported that mitral/tufted cells associated with the same glomerulus projected to patches in PC. Such findings suggest that the representation of glomerular input to PC may have a higher degree of topographical organization than previously suspected. However, odor responses in PC, as determined by Fos mapping, do not show discrete patches, perhaps indicating that a restricted afferent input is distributed by intracortical processing (Illig and Haberly, 2003).

5.3.1.1 Neurochemistry of MOB Inputs The MOB projection to PC, via the mitral/tufted cells, is glutamatergic. Bulbectomy reduces evoked release of aspartate and NAG in PC (Collins and Probett, 1981a; Ffrench-Mullen et al., 1985) and stimulation of LOT induces glutamate and aspartate release in PC (Collins and Probett, 1981b). Receptor localization studies indicate that ionotropic glutamate and mGluRs are present in PC (*Table 6-6*). Stimulation of mitral/tufted cell axons in the LOT produces monosynaptic depolarization and spiking in superficial pyramidal cells. LOT-evoked excitation of PC is also blocked by DNQX (Collins and Buckley, 1989), a potent postsynaptic antagonist of kainate and AMPA receptors. By contrast, selective NMDA receptor antagonists do not reduce LOT-evoked monosynaptic excitation of PC cells. LOT-evoked responses in PC are attenuated by 2-amino-4-phosphonobutyric acid (AP4) (Collins, 1982; Hori et al., 1982; Ffrench-Mullen et al., 1985, 1986; Hasselmo and Bower, 1991), an agonist of Group III mGluRs. The AP4-induced suppression appears to be mediated by presynaptic inhibition of glutamate release from mitral/tufted cell axon terminals (Hasselmo and Bower, 1991), consistent with anatomical evidence that these cells express Group III mGluRs on their axon terminals. Collins and Richards (1990) reported that protein kinase inhibitors reduce LOT-evoked monosynaptic excitation of PC, further supporting a role for a metabotropic, second messenger-mediated regulation of excitatory transmission at this synapse.

5.3.2 Intrinsic and Association Connections

PC has extensive connections, including (1) intrinsic, local, short translaminar connections between neurons in different layers of the PC, and (2) associative, longer-range, rostrocaudally directed connections with different parts of the PC.

5.3.2.1 Intrinsic or Local Connections There are extensive translaminar connections from superficial to deeper layers and vice versa. Layer II pyramidal cell axon collaterals synapse with deeper layer III pyramidal cells and with local inhibitory interneurons in layers I and II. Local collaterals from deeper pyramidal cells synapse with local interneurons or with more superficial pyramidal cells. Local projections from pyramidal cells to GABAergic interneurons play an important role in regulating PC neuronal excitability, including the expression of LTP and seizures, via feedback and feedforward inhibition (Ekstrand et al., 2001a).

5.3.2.2 Association Connections Cortico-cortical projections within PC are extensive and exhibit laminar and regional organization (Haberly and Price, 1978a, b; Luskin and Price, 1983). Axons from pyramidal cells of layer IIb are primarily directed at more caudal sites in PC, whereas pyramidal cells in layer III project predominantly to rostral parts of PC. Overall, the rostral-to-caudal associational connections are

heavier than the caudal-to-rostral directed counterparts. Both systems terminate more heavily within the lateral than the medial parts of PC (Datiche et al., 1996). The contralateral PC also receives commissural fibers that arise from layer IIb of the anterior parts of PC. All of these association fiber systems terminate in a highly laminar fashion in layer Ib, immediately below the zone that contains the afferent input from the MOB; a lighter projection terminates in layer III.

5.3.2.3 Features and Neurochemistry of a Simple Model of PC Network Operation The orderly laminar structure of the PC and the segregation of MOB and association fiber inputs in layer I facilitate the analysis of PC's physiological organization. Haberly and others have provided a detailed analysis of the site and sequence of synaptic responses mediated by afferent inputs (i.e., LOT) and associative circuits (Haberly and Shepherd, 1973; Satou et al., 1983a, b, c; Haberly and Bower, 1984; Rodriguez and Haberly, 1989). LOT-shocks, or shocks applied to layer Ib to activate association fibers, result in a volley of activity that sweeps sequentially through PC. Field-potential recording studies suggest that there is little spatial topography to the pattern of activity following LOT or association fiber shocks. Thus, activity spreads diffusely from the site of activation, both rostrally and caudally. Single LOT shocks elicit a field potential exhibiting monosynaptic (A1) and disynaptic (B1) excitatory components (Haberly and Shepherd, 1973; Rodriguez and Haberly, 1989). The A1 component reflects monosynaptic excitation of pyramidal cell apical dendrites by LOT fibers. The B1 component reflects disynaptic excitation of pyramidal cells mediated by association fibers. The A1 and B1, mono- and disynaptic components are mediated by glutamate acting at both AMPA/kainate and NMDA receptors (Collins, 1982; Collins and Buckley, 1989). Baclofen, a $GABA_B$ receptor agonist, inhibits responses elicited by association fibers, but not LOT fibers, via a presynaptic mechanism (Tang and Hasselmo, 1994). Feedback and feedforward inhibitory circuits within PC suppress repetitive firing from pyramidal cells, and hence, reactivation of intracortical excitatory circuits. Fast ($GABA_A$) and slow ($GABA_B$) feedforward inhibitory systems independently regulate the excitability of the pyramidal cell somata and apical dendrites (Tseng and Haberly, 1988; Kanter et al., 1996; Kapur et al., 1997). Selective blockade of the apical-dendritic inhibition enhances NMDA receptor-dependent afferent synaptic responses in pyramidal cells (Kanter et al., 1996). Computational modeling suggests that inhibitory circuits in PC operate to reiterate patterned oscillatory activity from the bulb. Slow $GABA_B$ receptor-mediated inhibition is thought to tune PC activity to the 3–10 Hz θ range while fast $GABA_A$ receptor-mediated inhibition provides tuning in the 40–50 Hz γ range (Wilson and Bower, 1992). Thus, at least part of the oscillatory activity emerges from intrinsic properties of intracortical inhibitory circuits.

5.4 Extrinsic Outputs of PC

Outputs of PC can be categorized into three main classes, which include: (1) MOB, (2) cortical structures, and (3) subcortical structures (*Figure 6-7*).

5.4.1 Feedback to the MOB

As noted earlier, PC and other structures of POC project heavily back to the MOB (*Figure 6-7*). These feedback projections are heavier from the rostral than the caudal parts of POC (Shipley and Adamek, 1984) and arise mainly from pyramidal neurons in layer II and to a lesser extent in layer III.

5.4.2 Cortical Projections

There are also direct projections from PC to insular and orbital cortex. Insular and orbital cortices are also the primary cortical targets of ascending pathways arising in the nucleus of the solitary tract in the medulla and appear to contain the primary cortical representations for both gustatory and visceral sensations. Thus,

olfactory projections to insular and orbital cortex may form a part of the circuitry that integrates olfactory and gustatory signals to generate the integrated perception of flavor.

5.4.3 Subcortical Projections

There are direct olfactory projections to the hypothalamus from neurons in the deepest layers of PC that terminate most heavily in the lateral hypothalamic area. Other components of PC project to medial and anterior parts of the hypothalamus and to the thalamus (Benjamin et al., 1982; Price and Slotnick, 1983).

5.5 Amino Acid Receptor Distribution in PC

5.5.1 Glutamate Receptors

Receptor localization studies indicate that layer II of PC contains an extensive amount of AMPA and kainate receptor subtypes, whereas layers Ia and II stain for NMDA receptors (Monaghan et al., 1985; Gall et al., 1990; Petralia and Wenthold, 1992; Wisden and Seeburg, 1993; Molnar et al., 1993; Petralia et al., 1994a, b). Receptors for mGluR1, mGluR2/3, mGluR5, mGluR7, and mGluR8 are present in PC (Shigemoto et al., 1992; Kinzie et al., 1995, 1997; Romano et al., 1995; Saugstad et al., 1997; Kinoshita et al., 1998; Wada et al., 1998). Pyramidal cells express mGluR1 (Shigemoto et al., 1992). Consistent with evidence that mGluR7-8 are presynaptically located on mitral/tufted cell axons, these receptors are densely expressed in layer Ia where these axons terminate (Kinzie et al., 1997; Kinoshita et al., 1998; Wada et al., 1998), and expression of mGluR7-8 was markedly decreased after bulbectomy or LOT transection. At the EM level, mGluR7 and 8 were found to be colocalized on axon terminals in layer Ia (Wada et al., 1998) (*Table 6-6*).

5.5.2 GABA Receptors

$GABA_A$ receptors are located in layers I and III of PC (Young and Kuhar, 1980b; Palacios et al., 1981b; Bowery et al., 1987). Although studies have shown intense staining for $GABA_A$ receptors, there is only a very weak signal $GABA_B$ receptors (Bowery et al., 1987).

5.6 Neuromodulatory Inputs to PC

5.6.1 Cholinergic Inputs to PC

5.6.1.1 Cholinergic Innervation Pattern and Receptor Distribution Cholinergic inputs to PC arise from NDB cells that are codistributed among, but are distinct from, those that project to MOB. Thus, the cholinergic inputs to MOB and PC originate from separate populations of NDB neurons. The distribution of cholinergic inputs along the rostrocaudal axis of PC is fairly homogenous (Lysakowski et al., 1989). Layer I receives a sparse cholinergic innervation, whereas layers II and III receive a moderate and fairly uniform cholinergic innervation; the density of fibers is somewhat heavier in layer II than III. All four muscarinic subtypes (M_1, M_2, M_3, and M_4) are present in layer II (Rotter et al., 1979; Spencer et al., 1986; Buckley et al., 1988). The M_1 receptor subtype has also been localized on dendritic spines in layer I, but the cell type was not specified (Levey et al., 1991). Nicotinic cholinergic receptors are located in layers II and III, but as with the muscarinic receptors, the cellular and dendritic locations of these receptors are not known (Sahin et al., 1992; Hill et al., 1993; Seguella et al., 1993) (*Table 6-6*).

5.6.1.2 Cholinergic Actions In PC slices, ACh and muscarinic cholinergic agonists suppress intrinsic (layer Ib) fiber transmission without affecting transmission at afferent (layer Ia) fiber synapses (Hasselmo and

Bower, 1992; Hasselmo et al., 1992b; Hasselmo et al., 1997). This suppression is presynaptically mediated by the M1 muscarinic subtype. Cholinergic agonists also appear to directly increase the excitability of pyramidal neurons, increasing neuronal bursts induced by intracellular depolarization. This effect is mediated, in part, by blockade of the slow afterhyperpolarization mediated by a Ca^{2+}-dependent K^{+} current. ACh, acting at muscarinic receptors, has been shown to reduce the M-current in PC pyramidal neurons (Constanti and Galvan, 1983), and to depolarize and increase the firing rate of pyramidal cells (Libri et al., 1994; Postlewaithe et al., 1998). In the later study, muscarinic receptor stimulation was also reported to induce a slow poststimulus afterdepolarization and to depress EPSPs elicited by association fibers. Activation of the NDB, which is the source of cholinergic projections to PC, in vivo increased the spontaneous firing rate of PC cells, and it also increased the disynaptic excitatory (B1), and decreased the disynaptic inhibitory (P2), field-potential components evoked by LOT stimulation (Zimmer et al., 1999). NDB stimulation decreased the P2 component following activation of association fibers in caudal PC, and also reduced the paired-pulse inhibition of the P2 component following LOT and caudal PC shocks. These effects were reversed by scopolamine, suggesting the involvement of muscarinic receptors. These results suggest that activation of cholinergic inputs to PC increases the excitability of pyramidal cells, probably by a disinhibitory mechanism. A subsequent in vivo study reported similar findings: NDB stimulation enhanced the late, disynaptic component of the evoked potential elicited by LOT stimulation, but caused a suppression of the synaptic potential elicited by stimulation of the posterior PC; both effects were antagonized by muscarinic receptor blockers (Linster et al., 1999). Other in vivo experiments utilizing optical imaging reported contrasting results suggesting that NDB stimulation reduced both mono- and disynaptic responses elicited by LOT stimulation; the mechanism and transmitter involved in these effects were not studied (Rosin et al., 1999). More recent in vivo experiments showed that topical application of muscarinic receptor antagonists did not alter spontaneous or odor-evoked activity of anterior PC cells (Wilson, 2001). However, these antagonists enhanced odor-evoked cross-habituation, perhaps indicating that ACh acts to enhance generalization between odor representations in PC.

5.6.2 Dopaminergic Inputs to PC

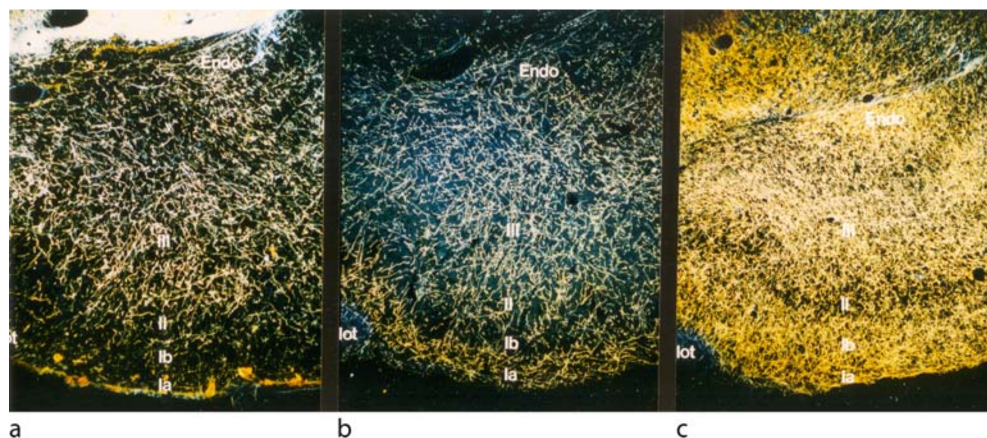
5.6.2.1 DA Innervation Pattern, Receptor Distribution, and Physiological Actions DA inputs to PC arise from several sources, including the substantia nigra, ventral tegmental area and, to a lesser extent, the rostrodorsal part of dorsal raphe nucleus (Datiche and Cattarelli, 1996). The dopaminergic innervation of PC exhibits a marked rostrocaudal gradient and laminar specificity (Datiche and Cattarelli, 1996). Rostrally, DA fibers are relatively sparse and primarily confined to layers II/III (*Figure 6-11*). Along the rostral-to-caudal axis of PC, the density of innervation progressively increases and DA fibers invade more superficial layers of PC. A moderately dense plexus of DA fibers extends from the deep part of layer I through layer III, to the caudal limit of PC. Autoradiographic, in situ hybridization and immunocytochemical studies have revealed the presence of D1 receptors in layer II (Palacios et al., 1981a; Mansour et al., 1990a, b; Fremeau et al., 1991; Huang et al., 1992). To date, there is little definitive evidence concerning the presence of D2 receptors in PC. Relatively little is known about DA functions in PC. DA was reported to excite PC interneurons, leading to increased IPSC activity in pyramidal cells (Gellman and Aghajanian, 1993, 1994).

5.6.3 Noradrenergic Inputs to PC

5.6.3.1 Noradrenergic Innervation Pattern and Receptor Distribution Noradrenergic LC neurons project heavily to PC and represent the major source of NE input to this structure (Fallon and Loughlin, 1982; Datiche and Cattarelli, 1996). LC lesions decrease NE levels in PC by 77% (Fallon and Moore, 1978). Like the projection to the neocortex, the LC projection to PC is primarily ipsilateral with a small contralateral component. Early histofluorescence studies (Fallon and Moore, 1978) of monoaminergic innervation of PC

Figure 6-11

Neuromodulatory transmitter inputs to PC. Darkfield photomicrographs showing the distribution of dopaminergic (a), noradrenergic (b), and serotonergic (c) fibers revealed respectively with immunohistochemistry for tyrosine hydroxylase (TH), dopamine-β-hydroxylase (DBH), and serotonin (5-HT). Abbreviations: Endo, endopiriform nucleus; lot, lateral olfactory tract. Reprinted from Handbook of Chem. Neuroanat. Integrated Sys. CNS, Vol. 12, Part III, Chapter III, The Olfactory System, M. Shipley et al., pp. 469–573, 1996, with permission from Elsevier, Ltd



could not unambiguously distinguish among 5-HT, DA, and NE fibers. Immunohistochemistry for the NE biosynthetic enzyme dopamine-β-hydroxylase (DBH) showed that layers Ia and III of PC contained a moderate plexus of NE fibers; layer II was sparsely innervated (*Figure 6-11*) (Datiche and Cattarelli, 1996). A distinctive feature of NE innervation of PC is the long fibers oriented primarily parallel to the pial surface in layer Ia. The density and laminar distribution of NE fibers are relatively uniform along the rostrocaudal axis of PC (Datiche and Cattarelli, 1996).

Both α and β receptors are present in PC (*Table 6-6*). $\alpha1$-receptors are highly expressed in layers II/III (Sargent-Jones et al., 1985) and layer II pyramidal cells express high levels of $\alpha1_A$, $\alpha1_B$, and low levels of $\alpha1_D$ (Pieribone et al., 1994; Day et al., 1997; Domyancic and Morilak, 1997). High levels of $\alpha2$ receptor binding sites are present in PC (Young and Kuhar, 1979, 1980a; Unnerstall et al., 1984; Winzer-Serhan et al., 1997a), and $\alpha2_A$ and $\alpha2_C$ appear to be expressed by layer II pyramidal cells (Nicholas et al., 1993; Rosin et al., 1996; Talley et al., 1996; Winzer-Serhan et al., 1997a, b); $\alpha2_C$ receptors appear to be expressed by neurons in all layers of PC (Rosin et al., 1996). Weak-to-moderate expression of β receptor subtypes has also been reported (Palacios and Kuhar, 1982; Wanaka et al., 1989).

5.6.3.2 Physiological Actions of NE Early field-potential studies reported that low concentrations of NE (0.1–5 μM) enhanced, and high concentrations (20–250 μM) suppressed, LOT-evoked responses in PC (Collins et al., 1984). These effects were blocked by both α and β receptor antagonists. A subsequent study reported uniform suppression of LOT-evoked field potentials by NE (1–100 μM), although the effects were greater in layer Ib than Ia (Hasselmo et al., 1997). These effects were similar to those elicited by carbachol. The cellular actions of NE on PC neurons have received relatively little attention. NE was shown to block the slow afterhyperpolarization in guinea-pig pyramidal cells (Constanti and Sim, 1987). NE was reported to excite putative interneurons located at the layer II/III border, which in turn, increased IPSC activity in pyramidal cells in vitro (Sheldon and Aghajanian, 1990; Gellman and Aghajanian, 1993, 1994). Other studies from the same laboratory indicated that the NE-induced interneuronal excitation was mediated by $\alpha1_B$ receptors (Marek and Aghajanian, 1996a). LC activation in vivo was found to enhance odor-evoked responses in anterior and posterior PC (Bouret and Sara, 2002).

5.6.4 Serotonergic Inputs to PC

5.6.4.1 5-HT Innervation Pattern and Receptor Distribution Anterograde and retrograde tracing studies have demonstrated a rich projection from the dorsal raphe nucleus to PC (De Olmos and Heimer, 1980; Vertes, 1991; Datiche et al., 1995). Ascending serotonergic fibers from the dorsal raphe terminating in PC are believed to travel in the ventrolateral aspect of the medial forebrain bundle (Azmitia and Segal, 1978). Anterograde labeling of ascending dorsal raphe axons demonstrated that the entire PC was targeted by raphe projections (Vertes, 1991; Datiche et al., 1996). The projection was reported to be heavier to rostral than caudal PC, and heavier to the deeper than the superficial layers. The transmitter of labeled fibers could not be identified in these anterograde tracing results. The serotonergic innervation of PC is very heavy by comparison to DA and NE. 5-HT fibers are especially heavy in layers I and III and in the endopiriform nucleus (*Figure 6-11*) (Datiche et al., 1996). The density of 5-HT fibers progressively decreases in the deeper parts of layer III. Layer II by contrast, is sparsely innervated.

Receptor binding and in situ hybridization studies suggest that 5-HT_{1A} receptors are located on the dendrites of pyramidal cells (layer II) and also on intrinsic cells of layer III (Pompeiano et al., 1992) (*Table 6-6*). 5-HT_{2A} and 5-HT_{2C} receptors are strongly expressed by layer II pyramidal cells, as well as by interneurons in layers II and III (Pompeiano et al., 1994; Hamada et al., 1998; Cornea-Hebert et al., 1999). The 5-HT_3 subtype is present in PC and colocalizes with diverse interneuronal subtypes (Tecott et al., 1993; Morales and Bloom, 1997). 5-HT_3 colocalizes with approximately 50% of CCK-positive interneurons, and it is also expressed by interneurons containing GABA or CR, but not PV (Morales and Bloom, 1997).

5.6.4.2 Physiological Actions of 5-HT 5-HT has several actions on PC pyramidal cells as well as on putative interneurons that are mediated by distinct 5-HT receptor subtypes (Sheldon and Aghajanian, 1990, 1991; Gellman and Aghajanian, 1994). 5-HT has mixed, but predominately excitatory actions on layer II pyramidal cells. This excitation appears to be mediated by a reduction of the M-current, a noninactivating voltage-dependent outward K^+ current, as well as a decrease in a Ca^{2+}-activated K^+ current. These actions appear to be mediated via 5-HT_{1C} receptors. 5-HT also inhibits and increases the frequency of IPSPs in other pyramidal cells. This is mediated by excitation of layer III GABAergic interneurons that are directly activated (i.e., depolarized) by 5-HT acting at the 5-HT_{2A} receptor subtype (Gellman and Aghajanian, 1994; Marek and Aghajanian, 1994, 1996b). Interneurons excited by 5-HT appear to be a distinct subset distinguished by a relatively depolarized resting membrane potential, higher input resistance, and short action potential duration. The 5-HT_{2A} receptor-mediated effects on interneurons were not blocked, but instead were enhanced, by inhibitors of PKC, suggesting that PKC negatively modulates the excitation of PC interneurons (Marek and Aghajanian, 1995). In vivo, layer III putative interneurons were inhibited by 5-HT_{2A} agonists (Bloms-Funke et al., 1999). It is unclear if and how these cells correspond to those studied in vitro by Aghajanian and colleagues.

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