a0005

# 2.44 Physiology of the Main Olfactory Bulb

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## Glossary

g0005 ***apamin*** A blocker of SK-type potassium channels.

g0010 ***AP5*** An NMDA receptor antagonist.

g0015 ***CNQX*** An AMPA receptor antagonist.

g0020 ***field potentials*** Extracellularly recorded voltages represented summed currents from a population of neurons.

***gabazine*** A $GABA_A$ receptor antagonist. g0025

***ZD 7288*** A blocker of Ih channels. g0030

***4-AP*** A blocker of A-type potassium channels ($I_A$). g0035

## Abbreviation

| | |
|---|---|
| **ADPs** | afterdepolarizations |
| **DA** | dopamine |
| **EPL** | external plexiform layer |
| **ET cells** | external tufted cells |
| **GCL** | granule cell layer |
| **GL** | glomerular layer |
| **HVA** | high-voltage-activated |
| **IAS** | intrabulbar association system |
| **IPL** | internal plexiform layer |
| **JG cells** | juxtaglomerular cells |
| **LC** | locus coeruleus |
| **LLDs** | long-lasting depolarizations |
| **LOT** | lateral olfactory tract |
| **LTS** | low-threshold $Ca^{2+}$ spike |
| **LVA** | low-voltage-activated |
| **MCL** | mitral cell layer |
| **MOB** | main olfactory bulb |
| **NADPH** | nicotinamide adenine dinucleotide phosphate |
| **NDB** | nucleus of the horizontal limb of the diagonal band |
| **NE** | norepinephrine |
| **NPY** | neuropeptide-Y |
| **ON** | olfactory nerve |
| **ORNs** | olfactory receptor neurons |
| **PG cells** | periglomerular cells |
| **PLAP** | placental alkaline phosphatase |
| **POC** | primary olfactory cortex |
| **RMS** | rostral migratory stream |
| **SA cells** | short axon cells |
| **TH** | tyrosine hydroxylase |
| **TRH** | thyrotropin-releasing hormone |
| **VIP** | vasoactive intestinal polypeptide |

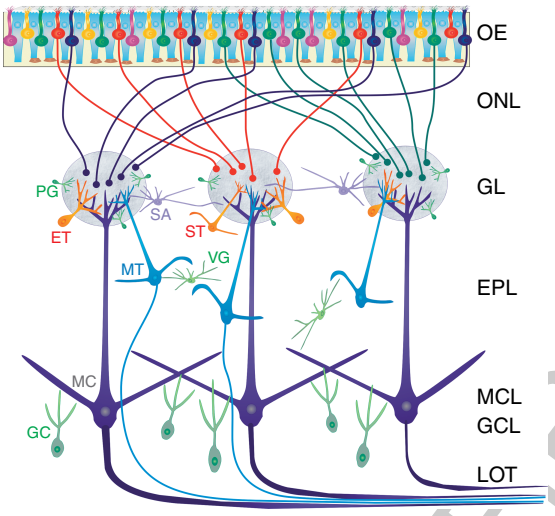
## s0005 2.44.1 Overview of Main Olfactory Bulb Circuitry

### s0010 2.44.1.1 Projections of Olfactory Receptor Neurons to Main Olfactory Bulb

p0005 As discussed elsewhere, odors are transduced by olfactory receptor neurons (ORNs), giving rise to AU1 action potentials. The action potentials propagate along the axons of ORNs – the olfactory nerve (ON) fibers. These fibers form bundles which then collect as groups of fascicles, pass through the cribriform plate, and synapse in the main olfactory bulb (MOB). Within the MOB, ON axons terminate and synapse with neural elements in the glomerular layer (GL). Based on anatomical considerations (high packing density of unmyelinated axons), it has been speculated that ephaptic interactions (current spread through the extracellular space) might synchronize ON fibers. Computational modeling studies (Bokil, H. *et al.*, 2001) suggest that spikes in a single ON axon evoke spikes in adjacent axons, thus leading to synchronous firing of a large number of axons. These findings suggest that ephaptic interactions among neighboring axons may synchronize

spikes among ON fibers converging on the same glomerulus.

p0010 ORNs expressing the same odorant receptor project to one or two glomeruli located on the medial and/or lateral side of each MOB (Figure 1; Ressler, K. J. *et al.*, 1993; 1994; Vassar, R. *et al.*, 1994; Mombaerts, P. *et al.*, 1996; Wang, F. *et al.*, 1998; Potter, S. M. *et al.*, 2001; Treloar, H. B. *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, P. *et al.*, 1996; Wang, F. *et al.*, 1998; Potter, S. M. *et al.*, 2001; Treloar, H. B. *et al.*, 2002). Rough calculations confirm an approximately 1:2 ratio between the number of different types of receptors (~1000) and the total number of glomeruli (~1800) in mice.




f0005 **Figure 1** Schematic illustration of the basic circuitry of the main olfactory bulb (MOB) including the projections of olfactory receptor neurons (ORNs) from the olfactory epithelium (OE) to the glomerular layer (GL). Note that ORNs expressing different odorant receptor genes (shown as blue, red, or green cells) are interspersed and widely distributed, yet the axons of ORNs expressing the same odorant receptor gene converge onto the same glomerulus (or pairs of medial and lateral glomeruli) in the GL. Axons of ORNs travel in the olfactory nerve layer (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 (PG) cells, ET cells, and short axon (SA) cells. 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 (ST) cells 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. The majority of GCs are concentrated in the GC layer (GCL) but a few lie within 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 (VG) cells within the EPL. AU2

p0015 ORNs utilize glutamate as their primary neurotransmitter (Sassoe-Pognetto, M. *et al.*, 1993). AU3 AU4 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, D. and Margolis, F. L., 1975; Margolis, F. L., 1980; Biffo, S. *et al.*, 1990). AU5 Carnosine colocalizes with glutamate in the ON axon terminals (Sassoe-Pognetto, M. *et al.*, 1993), and it satisfies criteria for neurotransmitter AU6 AU7 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; (3) high-affinity binding sites for carnosine are present in the GL (Ferriero, D. and Margolis, F. L., 1975; Margolis, F. L., 1980; Burd, G. D. *et al.*, 1982; Rochel, S. and Margolis, F. L., 1982; Margolis, F. L. *et al.*, 1983; Margolis, F. L. and Grillo, M., 1984; Margolis, F. L. *et al.*, 1985; 1987; Biffo, S. *et al.*, 1990). Zinc and copper are also present in high concentrations in ON axon terminals (Biffo, S. *et al.*, 1990). The potential neuromodulatory roles of carnosine, zinc, and copper are discussed below.

### 2.44.1.2 MOB Circuitry

s0015

p0020 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 ON layer (ONL), GL, external plexiform layer (EPL), mitral cell layer (MCL), internal plexiform layer (IPL), granule cell layer (GCL), and the ependymal layer (Figure 1). The ONL consists of ON axons and glial cells (Cajal, R. S. Y., 1911a; 1911b; Pinching, A. J. and Powell, T. P., 1971b; Doucette, R., 1989). Deep to the ONL, the GL is comprised of neutropil-rich ovoid structures – the glomeruli – each of which is surrounded by a shell of small neurons and glia. Within the glomeruli, ON axons form synapses with mitral and tufted cells, as well as with the intrinsic neurons of the GL – the

juxtaglomerular (JG) cells. Adjacent glomeruli are somewhat isolated from each other by astrocytes residing in the glomerular shell (Bailey, M. S. and Shipley, M. T., 1993). 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. The EPL also contains several subtypes of tufted cells and intrinsic interneurons. The dominant feature of the EPL is nevertheless the extensive dendrodendritic synapses between mitral/tufted cells and GCs. Deep to the EPL, the MCL is a thin layer that contains the somata of mitral cells, as well as numerous GCs (Cajal, R. S. Y., 1911a; 1911b). Together with tufted cells, mitral cells are the major class of output cells of the bulb. They extend a single apical dendrite into the GL, where it arborizes extensively throughout much of a single glomerulus (Figure 1). The apical dendrites are synaptically contacted by ON terminals (Price, J. L. and Powell, T. P. S., 1970a; Shepherd, G. M., 1972). The secondary or lateral dendrites of mitral cells ramify in the EPL where they form dendrodendritic synapses with dendrites of GCs. Mitral/tufted cell axons terminate within the bulb in the IPL and GCL (Mori, K. *et al.*, 1983; Price, J. L. and Powell, T. P. S., 1970c), or exit the MOB and innervate a number of olfactory-related brain regions collectively known as the primary olfactory cortex (POC). Deep to the MCL, the IPL is the relatively thin layer with a low density of cells. 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. The GCs are inhibitory GABAergic cells that form dendrodendritic synapses with mitral/tufted cells in the EPL.

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## 2.44.2 Neurophysiology of the Glomerular Layer

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### 2.44.2.1 Neurophysiological Properties of Glomerular Layer Neurons

p0025 The neurons of the GL are classified into three cell types, which include: (1) periglomerular (PG) cells, (2) external tufted (ET) cells, and (3) short axon (SA) cells (Golgi, C. 1875; Van Gehuchten, L. E. and Martin, A., 1891; Blanes, T., 1898; Cajal, R. S. Y., 1911a; 1911b; Pinching, A. J. and Powell, T. P., 1971a; 1971b; 1971c; 1972b; 1972c). Collectively, the intrinsic neurons of the GL are referred to as JG cells. The term JG is also used here with regard to cited studies in which the subtype of glomerular neuron was not specified. The morphology and features of these cells are only briefly reviewed here as more detailed descriptions are available (Hayar, A. *et al.*, 2004a; 2004b).

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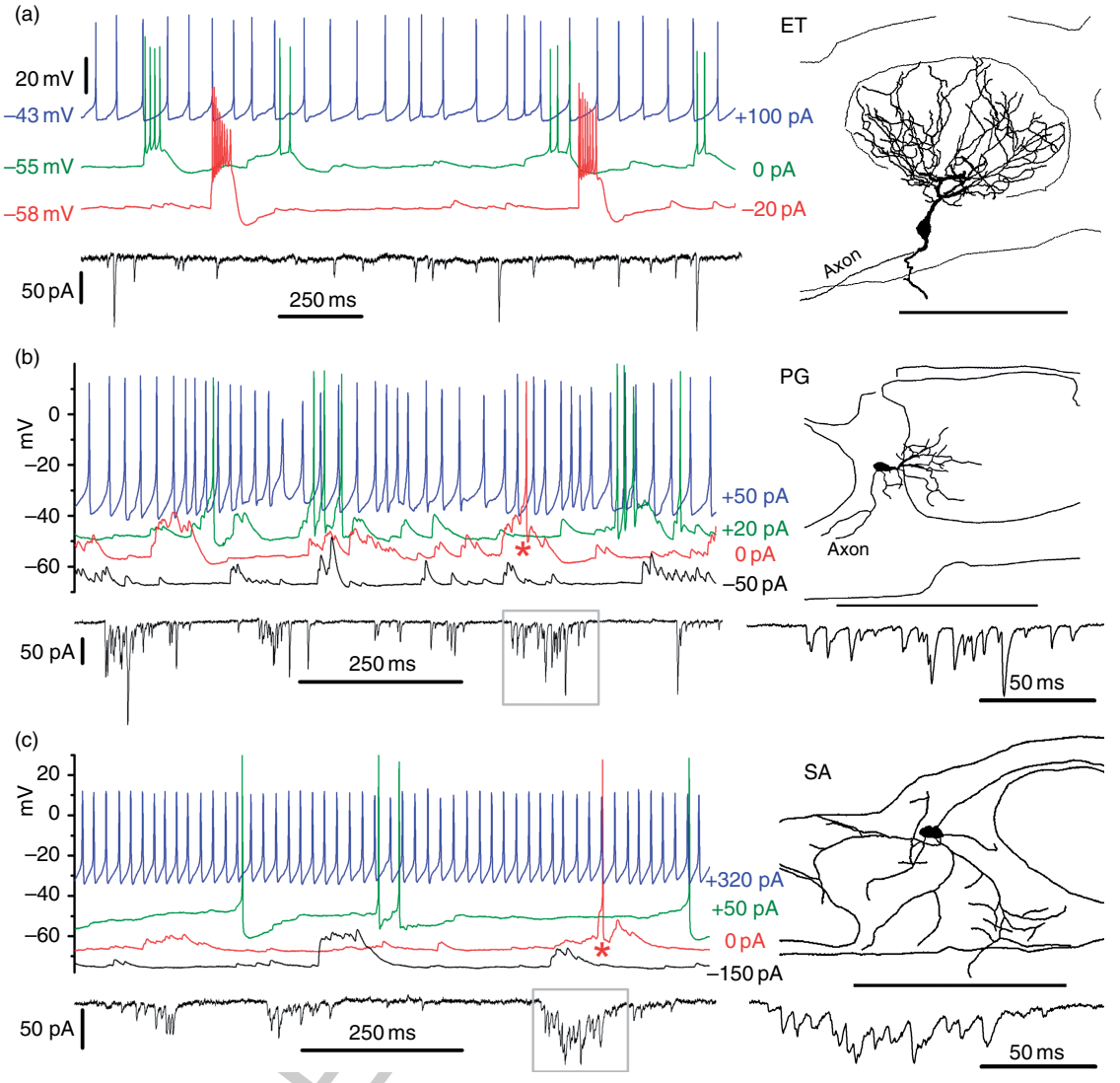
#### 2.44.2.1.1 ET cells

p0030 These are relatively large (10–15 μm) cells that are dispersed in the JG regions surrounding/deep to the glomeruli (Figures 1 and 2). Most have one apical dendrite that arborizes extensively throughout one glomerulus (Pinching, A. J. and Powell, T. P., 1971a; Hayar, A. *et al.*, 2004a; 2004b). 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, A. J. and Powell, T. P., 1971a). ET cells are somewhat similar to tufted cells of the EPL and to mitral cells, but growing evidence suggests that all tufted cell subtypes exhibit distinct anatomical and physiological properties.

p0035 The most distinctive physiological feature of ET cells is their spontaneous rhythmical bursting (Hayar, A. *et al.*, 2004a; 2004b; 2005) (Figure 2). JG cells with burst characteristics have been reported *in vivo* (Getchell, T. V. and Shepherd, G. M., 1975; Wellis, D. P. and Scott, J. W., 1990). However, because of the difficulty of recording small JG neurons *in vivo*, the identity of these cells and the basis of their bursting behavior remained unknown. The rhythmical burst-firing mode was characteristic of morphologically confirmed ET neurons (Hayar, A. *et al.*, 2004a). By contrast, PG and SA cells do not spontaneously generate spike bursts nor can they be induced to do so by intracellular current injections. Each ET cell bursts at its own characteristic frequency. As a population, ET cell burst frequencies range from ~1 to 8 Hz, with a mean of $3.3 \pm 0.18$ bursts/s. This range overlaps with the theta frequency range (2–12 Hz) prominent in oscillatory neural activity in the rodent olfactory network (see Oscillations and Synchrony in Main Olfactory Bulb); the theta range includes components related to low frequency (1–3 Hz) passive sniffing as well as a higher frequency component (5–10 Hz) characteristic of active investigative sniffing (Adrian, E. D., 1950; Welker, W. I., 1964; Macrides, F. *et al.*, 1982; Eeckman, F. H. and Freeman, W. J., 1990; Kay, L. M. and Laurent, G., 1999; Kay, L. M., 2003). ET cells also receive spontaneous bursts of IPSCs from PG cells AU9




f0010 **Figure 2** External tufted (ET) cells spontaneously generate rhythmic spike bursts, whereas periglomerular (PG) and short axon (SA) cells receive spontaneous bursts of excitatory synaptic input. Panels (a), (b), and (c) show the typical electrophysiological and morphological features of an ET, a PG, and a SA cell, respectively. The ET cell has highly branched tufted dendrites that ramify throughout a single glomerulus. The PG cell has relatively small soma and one to three relatively thick primary dendritic shafts that give rise to thinner branches ramifying within a subregion of a single glomerulus. The SA cell has several poorly branched dendrites that extended into or between two and four glomeruli. Scale bars below drawings, 100 μm. Current clamp recordings show resting spontaneous activity and effects of current injections. At rest (0 pA), the ET cell generates spontaneous bursts of spikes, whereas the PG and SA cells receive spontaneous bursts of EPSPs and generates spikes infrequently (asterisks). Bottom traces in a, b, and c show voltage-clamp recordings (holding potential = −60 mV) of spontaneous EPSCs in the same cells; regions enclosed in the box in b and c are shown at faster timescale at right. Note the bursting pattern of EPSCs in the PG and SA cells. Modified from Hayar, A. *et al.*, 2004, J. Neurosci. AU8 24, 6676–6685, with permission from The Society for Neuroscience.



(Hayar, A. *et al.*, 2005). ON stimulation evokes an EPSC in ET cells that is followed by IPSC bursts (Hayar, A. *et al.*, 2005). Both the spontaneous and ON-evoked IPSCs in ET cells are driven primarily by activation of AMPA receptors.

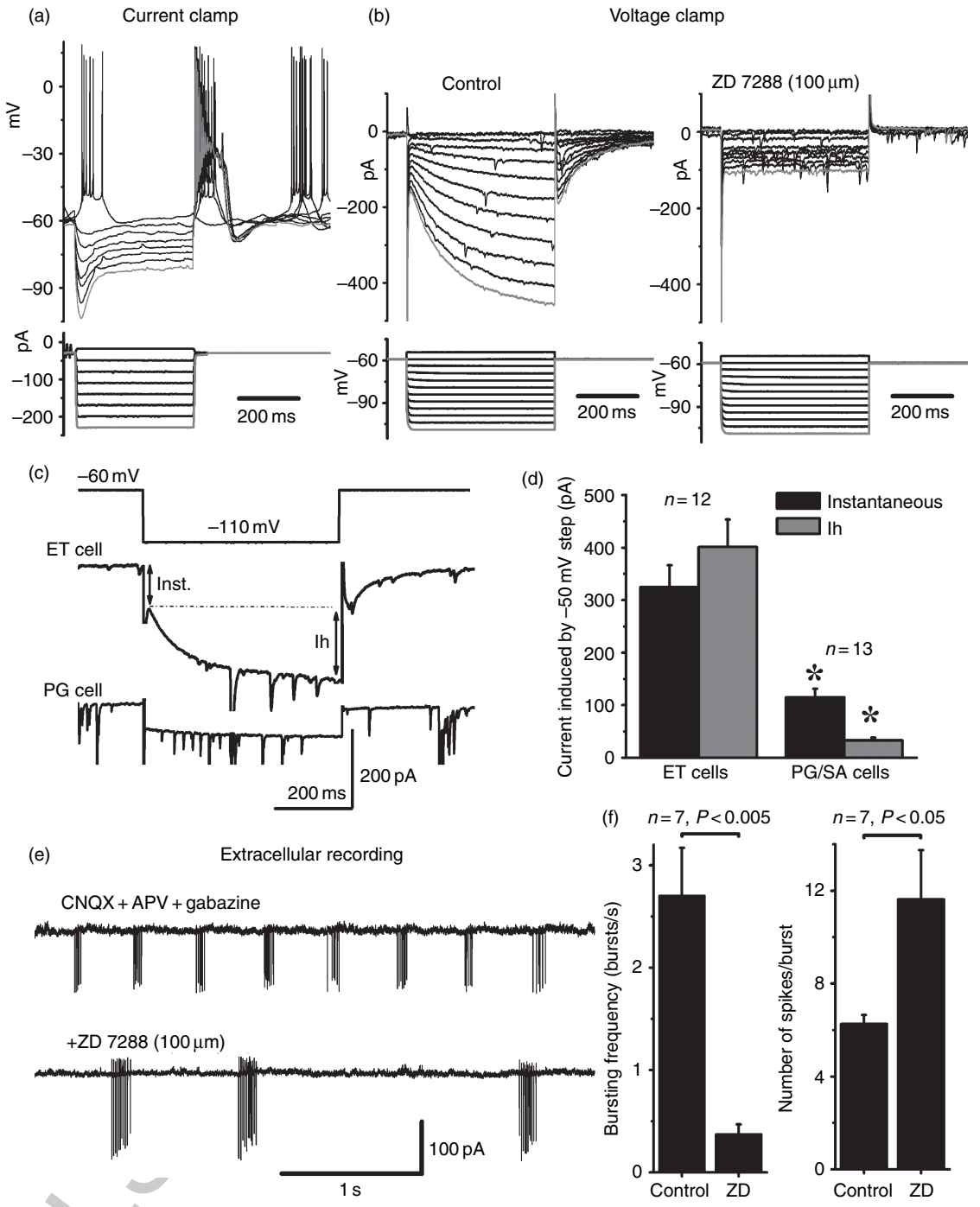
p0040 Several lines of evidence indicate that bursting is an intrinsic property of ET cells. First, bursting

deteriorates rapidly after establishment of whole-cell recording mode. This pronounced rundown of bursting may explain the low reported incidence of spontaneous bursting in JG cells in some whole-cell recording studies (Bardoni, R. *et al.*, 1995; Puopolo, M. and Belluzzi, O. 1996; McQuiston, A. R. and Katz, L. C., 2001). The rundown of bursting could be due to intracellular dialysis of an intracellular messenger important to maintain spontaneous activity (Alreja, M. and Aghajanian, G. K., 1995). Additional evidence in support of the intrinsic mechanism for bursting are the findings that: (1) burst frequency is voltage dependent and (2) bursting persists in blockers of glutamate and $GABA_A$ receptors. This eliminates the possibility that bursting is driven by glutamatergic input from the ON, glutamatergic dendrodendritic interactions among ET cells and/or mitral cells, or by disinhibition (Aroniadou-Anderjaska, V. *et al.*, 1999b; Isaacson, J. S., 1999; Carlson, G. C. *et al.*, 2000; Friedman, D. and Strowbridge, B. W., 2000; Salin, P. A. *et al.*, 2001; Schoppa, N. E. and Westbrook, G. L., 2001). Moreover, spontaneous bursting was not blocked by $Cd^{2+}$, which suppresses $Ca^{2+}$-dependent neurotransmitter release, ruling out the potential involvement of other neurotransmitters. Depolarizing current injections evoke in ET cells a low-threshold $Ca^{2+}$ spike (LTS) that was eliminated by the $Ca^{2+}$ channel blockers, $Cd^{2+}$ and $Ni^{2+}$ (McQuiston, A. R. and Katz, L. C., 2001; Hayar, A. *et al.*, 2004a). This suggested that the LTS might generate ET cell bursting. However, this is unlikely for several reasons. First, bursting in ET cells persisted after the LTS was blocked. Second, ET cell bursting was abolished by extracellular TTX or by intracellular QX-314, whereas the LTS persisted. Third, the activation threshold of the LTS (−38 mV) was approximately 15 mV more depolarized than the membrane potential from which bursting arises, on average −53 mV. $Ca^{2+}$ may modulate bursting as $Ca^{2+}$ channel blockers prolonged burst duration (Hayar, A. *et al.*, 2004a). $Ca^{2+}$ channel blockers also increased the interburst interval, but this could be due to a charge screening effect. Moreover, ET cells have a hyperpolarization-activated cation conductance (Ih) that is prominent at resting membrane potential (Figure 3). Ih current was found in all JG cells (Cadetti, L. and Belluzzi, O., 2001). However, other results (Hayar, A., unpublished observations) indicate that Ih is very strong in ET cells compared to PG and SA cells and that it contributes to tonic depolarization of ET cells because the specific Ih blocker, ZD 7288, significantly reduced the bursting frequency (Figure 3). Ih participates in burst timing and rhythmicity in other brain structures (DiFrancesco, D. 1993; Lüthi, A. and McCormick, D. A. 1998; Pape, H. C. 1996) and is modulated by $Ca^{2+}$. Thus, Ih and $Ca^{2+}$ may play a role in burst termination and/or setting the interburst interval.

Rhythmic bursting, but not the LTS, was blocked by extracellular TTX and by intracellular dialysis with QX-314. These results suggest that, as for many neocortical neurons (Brumberg, J. C. *et al.*, 2000), burst generation in ET cells requires slowly inactivating $Na^+$ channels, i.e., a persistent $Na^+$ current. Indeed, all ET cells tested had a prominent TTX-sensitive, persistent $Na^+$ current. The characteristics of this current are well suited to trigger spontaneous bursting in ET cells. The inward current activates near −60 mV, slightly hyperpolarized to the mean ET cell resting potential (−52 mV). Thus, it is reasonable to conjecture that as this persistent $Na^+$ current slowly depolarizes the ET cell membrane, additional $Na^+$ channels are activated further depolarizing the membrane to the threshold for action potential generation. This current maintains a level of depolarization sufficient to generate additional action potentials until another mechanism(s), possibly involving $Ca^{2+}$ (see above), terminates the burst by transiently hyperpolarizing the membrane below the activation threshold for the persistent $Na^+$ current. As the membrane repolarizes, the persistent $Na^+$ current is re-engaged, and the burst cycle is repeated.

#### 2.44.2.1.2 PG cells

These cells are the most numerous cells in the GL, and they are thought to be inhibitory in nature. They are small (5–8 μm), spherical or ovoid, and they are distributed in the PG regions surrounding the glomeruli (Figures 1 and 2). Their dendrites are typically restricted to a small subregion of a glomerulus (Pinching, A. J. and Powell, T. P., 1971a; Hayar, A. *et al.*, 2004a; 2004b). Their dendrites receive asymmetrical (morphologically excitatory) synapses from ET and mitral/tufted cell dendrites; only a relatively small subpopulation of PG cells receives synapses from ON terminals. Some of the mitral/tufted cell synapses are paired with reciprocal symmetrical (morphologically inhibitory) synapses back onto the parent mitral/tufted cell dendrites (Pinching, A. J. and Powell, T. P., 1971b; Toida, K. *et al.*, 1998; Kasowski, H. J. *et al.*, 1999; Toida, K. *et al.*, 2000). Physiological recordings indicate that PG cells also receive monosynaptic dendrodendritic excitatory input from ET cells (Hayar, A. *et al.*, 2004b). The




f0015 **Figure 3** External tufted (ET) cells have a prominent Ih current. (a) Responses of an ET to hyperpolarizing and depolarizing current steps (bottom) in current clamp mode. Note the sag induced by membrane hyperpolarization, indicative of the presence of Ih current. After releasing the cell from the hyperpolarizing current, a rebound burst of spikes occurred. (b) Response of the same cell to membrane voltage steps (bottom) in voltage-clamp mode. A time-dependent inward current (Ih) was produced with hyperpolarizing voltage steps (<− 70 mV) followed by a rebound smaller inward current, which were blocked by the selective Ih current blocker, ZD 7288. (c) A periglomerular (PG) cell exhibits a much smaller Ih current (in response to a hyperpolarizing step from −60 to −110 mV, voltage-clamp mode) than an ET cell. (d) Group data show that ET cells have significantly larger Ih current than PG and short axon (SA) cells. The instantaneous current (Inst) reflects the membrane conductance which is larger in ET cells, indicating that PG/SA cells have on average a relative much higher input resistance. (e) The bursting frequency of an extracellularly recorded spontaneously bursting ET cell (in the presence of CNQX, AP5, and gabazine) decreased in response to application the Ih blocker ZD 7288. However, the number of spikes/burst increased as shown in the grouped data in (f).

AU11

axons of PG cells are rare but have been reported to extend over distances equivalent to four to five glomeruli (Blanes, T., 1898; Pinching, A. J. and Powell, T. P., 1971a; Hayar, A. *et al.*, 2004a). They appear to form symmetrical (morphologically inhibitory) synapses onto mitral/tufted cell dendrites and onto ET cells and other JG cells (Pinching, A. J. and Powell, T. P., 1971c). Most PG cells are GABAergic (Ribak, C. E. *et al.*, 1977; Mugnaini, E. *et al.*, 1984; Kosaka, T. *et al.*, 1985; 1987a; 1987b; 1987c; 1987d; 1988). 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, N. *et al.*, 1977; Davis, B. J. and Macrides, F., 1983; Halász, N. *et al.*, 1985; Gall, C. *et al.*, 1986; McLean, J. H. and Shipley, M. T., 1988). About 80% of the DA cells contain GABA, which corresponds to about 50% of GABAergic cells (Kosaka, T. *et al.*, 1985; Gall, C. M. *et al.*, 1987; Kosaka, T. *et al.*, 1987a; 1987c; 1988; 1995). Therefore, the DA PG neurons are regarded as a subpopulation of GABAergic neurons. Some PG cell subtypes also stain for thyrotropin-releasing hormone (TRH), enkephalin, nicotinamide adenine dinucleotide phosphate (NADPH)-diaphorase, neuropeptide-Y (NPY), somatostatin, and vasoactive intestinal polypeptide (VIP) (Bogan, N. *et al.*, 1982; Davis, B. J. *et al.*, 1982; Gall, C. *et al.*, 1986; Scott, J. W. *et al.*, 1987; Merchenthaler, I. *et al.*, 1988; Tsuruo, Y. *et al.*, 1988; Sanides-Kohlrausch, C. and Wahle, P., 1990a; Davis, B. J., 1991; Alonso, J. R. *et al.*, 1993; Kosaka, T. *et al.*, 1987d; 1995; 1998).

p0055 The spontaneous activity patterns of PG and SA cells differ markedly from ET cells. PG and SA cells have relatively low levels of spontaneous spike activity and lack the capacity to generate spike bursts in response to depolarizing currents (Figure 2) (Hayar, A. *et al.*, 2004a; 2004b). In slices, spikes in PG cells are driven primarily by spontaneous glutamatergic excitatory postsynaptic potentials (EPSPs). However, because of their heterogeneous neurochemical characteristics, PG cells are also likely to be functionally heterogeneous. For example, some studies have reported that different PG cell subtypes appear to exhibit different $K^+$ conductances (Puopolo, M. and Belluzzi, O. 1998) as well as different firing behaviors (McQuiston, A. R. and Katz, L. C., 2001). An estimated 10% of PG neurons in adulthood are positive for tyrosine hydroxylase (TH) (McLean, J. H. and Shipley, M. T., 1988; Kratskin, I. and Belluzzi, O., 2003), the rate-limiting enzyme for DA synthesis. Dopaminergic neurons have been recently identified *in vitro* using a transgenic mouse strain harboring an eGFP (enhanced green fluorescent protein) reporter construct under the promoter of TH. The most prominent feature of these cells when recorded in acutely dissociated cell culture preparations was the presence of regular spontaneous spiking at ~8 Hz. In these cells, five main voltage-dependent conductances were identified (Pignatelli, A. *et al.*, 2005): the two having largest amplitude were a fast transient $Na^+$ current and a delayed rectifier $K^+$ current. In addition, they have three smaller inward currents, sustained by $Na^+$ ions (persistent type) and by $Ca^{2+}$ ions (low-voltage-activated (LVA) and high-voltage-activated (HVA)). The pacemaking activity was shown to be supported by the interplay of the persistent $Na^+$ current and of a T-type $Ca^{2+}$ current. Transgenic mice in which catecholaminergic neurons expressed human placental alkaline phosphatase (PLAP) on the outer surface of the plasma membrane were also used to identify dissociated dopaminergic PG neurons (Puopolo, M. *et al.*, 2005). Dopaminergic PG cells spontaneously generated action potentials in a rhythmic fashion with an average frequency of 8 Hz. It was found that substantial $Ca^{2+}$ current and TTX-sensitive $Na^+$ current flow during the interspike depolarization. These results show that dopaminergic PG cells have intrinsic pacemaking activity, supporting the possibility that they can maintain a tonic release of DA to modulate the sensitivity of the olfactory system during odor detection.

#### 2.44.2.1.3 SA cells

s0040

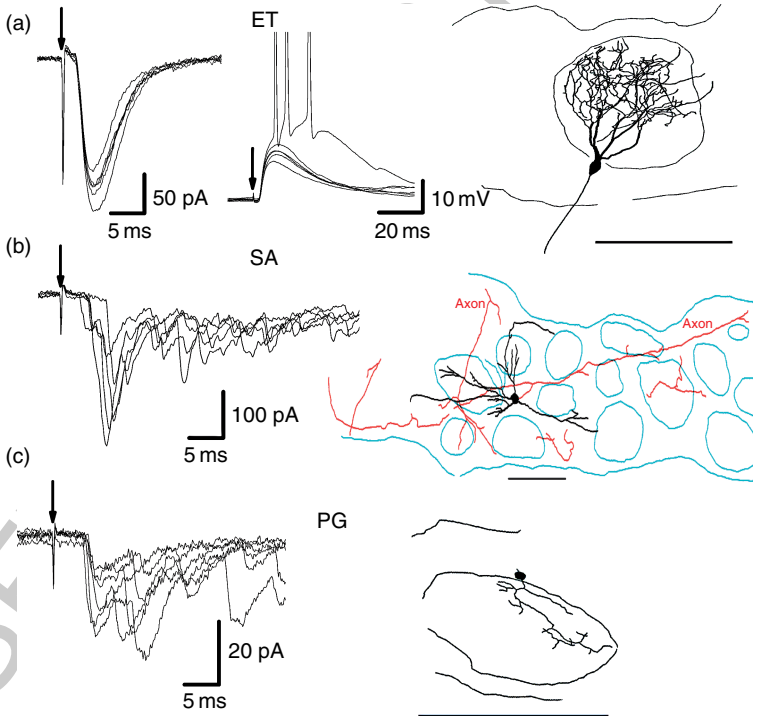
p0060 These cells are roughly the same size (8–12 μm) as ET cells. They are distinguished by multiple dendrites that seem to harvest information from multiple glomeruli (Figures 1 and 2) (Hayar, A. *et al.*, 2004b). The dendrites may receive synaptic inputs from ET cell dendrites (Hayar, A. *et al.*, 2004b), tufted cell collaterals, or other SA cells. SA cells have axons that can extend up to 1–2 mm within the GL (Aungst, J. L. *et al.*, 2003). The axons appear to synapse onto the dendrites of PG cells (Pinching, A. J. and Powell, T. P., 1971a). They do not receive direct ON input (Pinching, A. J. and Powell, T. P., 1971c; Hayar, A. *et al.*, 2004b). Their resting spontaneous activity patterns in MOB slices appear to be very similar to that of PG cells (Hayar, A. *et al.*, 2004b).

s0045 ## 2.44.2.2 Electrophysiology of Intraglomerular Circuitry

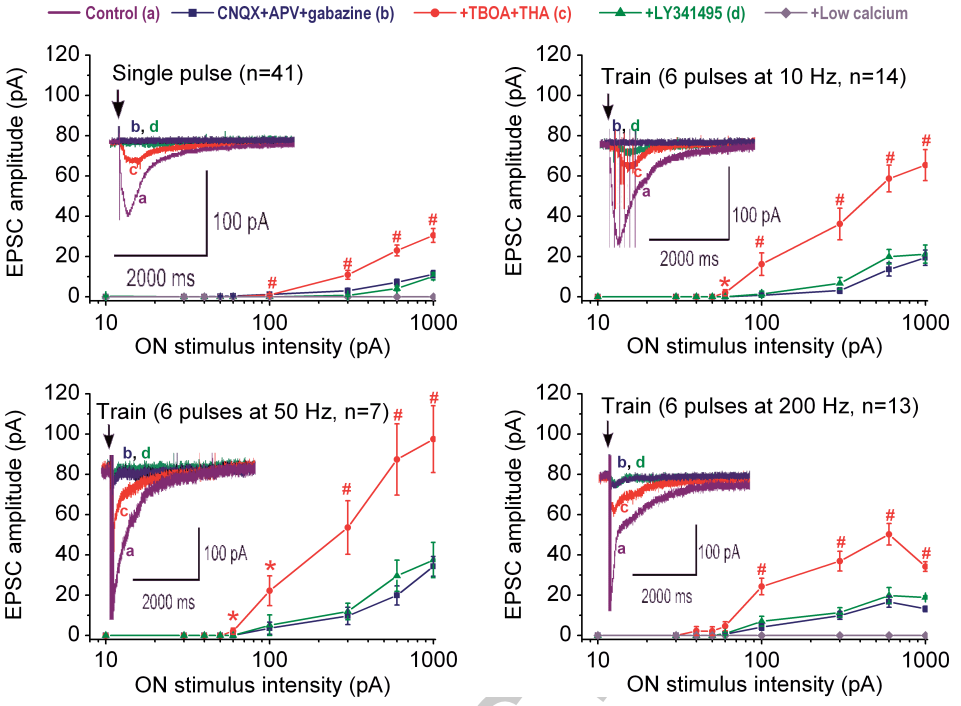
s0050 ### *2.44.2.2.1 Excitatory systems in the GL*

s0055 #### *2.44.2.2.1.(i) ON glutamatergic synaptic input to JG and mitral/tufted cells*

p0065 All studies to date have identified glutamate as the major transmitter at ON synapses onto the dendrites of JG neurons, as well as those of mitral/tufted cells in the GL. Release of glutamate from ON terminals is controlled by N- and P/Q-type $Ca^{2+}$ channels (Isaacson, J. S. and Strowbridge, B. W., 1998; Murphy, G. J. *et al.*, 2004). Each glomerulus contains the apical dendritic tufts of about 20 mitral cells, 200 tufted cells, and 1500–2000 AU12 JG cells (reviewed in Ennis, M. *et al.*, in press). A variety of studies demonstrated that sensory transmission from ON axon terminals to these dendrites is mediated by glutamate acting primarily at AMPA and NMDA ionotropic glutamate receptor subtypes (Bardoni, R. *et al.*, 1996; Ennis, M. *et al.*, 1996; Aroniadou-Anderjaska, V. *et al.*, 1997; Chen, W. R. and Shepherd, G. M., 1997; Keller, A. *et al.*, 1998; Aroniadou-Anderjaska, V. *et al.*, 1999a; Ennis, M. *et al.*, 2001). Thus, JG and mitral/tufted cell responses to ON input are excitatory (Figures 4 and 5). In addition, metabotropic glutamate receptors (mGluRs) are expressed by nearly all MOB neurons (see Ennis, M. *et al.*, in press for review). Comparatively less is known about the role of mGluRs at ON synapses. Electrophysiological and $Ca^{2+}$-imaging studies have reported that ON stimulation evokes an mGluR1-sensitive synaptic component in ~40% of mitral cells in normal physiological conditions in the slice (De Saint Jan, D. and Westbrook, G. L., 2005; Ennis, M. *et al.*, 2006; Yuan, Q. and Knopfel, T., 2006). In the presence of ionotropic glutamate receptor antagonists, ON-evoked, mGluR1-mediated synaptic responses were markedly enhanced by




f0020 **Figure 4** Olfactory nerve (ON)-evoked synaptic responses in juxtaglomerular (JG) cell subtypes. Panels a–c show six superimposed voltage-clamp traces (holding potential = −60 mV in this and subsequent panels) of ON-evoked EPSCs in external tufted (ET), short axon (SA), and periglomerular (PG) cells, respectively. Arrows indicate time of stimulation. Cell morphology is shown at right. Scale bars, 100 μm. ON stimulation produced short, constant latency EPSCs in the ET cell (a, left panel), indicative of monosynaptic input. In current clamp, ON stimulation evoked a constant, short latency EPSPs of variable amplitude (a, middle panel). The largest EPSPs triggered the generation of a burst of action potentials (truncated for clarity). Panels b and c show that ON stimulation evoked longer, variable latency EPSCs bursts in SA (b) and PG (c) cells, indicative of di- or polysynaptic responses. Modified from Hayar, A. *et al.*, 2004, J. Neurosci. 24, 6676–6685., with permission from The Society for Neuroscience.




AU54

f0025 **Figure 5** Olfactory nerve (ON)-evoked EPSCs elicited in the presence of glutamate uptake inhibitors (TBOA and THA) are dependent on stimulation intensity and frequency. The four panels show plots of the peak amplitude of ON-evoked EPSCs as a function of ON stimulation intensity (10–1000 μA); each panel shows data for a different ON stimulation frequency. Insets in each graph show traces of ON-evoked EPSCs in different pharmacological conditions; traces are averages of five ON-evoked EPSCs. Colored lines correspond to the pharmacological conditions indicated at the top; note that control data are not plotted on the line graphs. TBOA–THA significantly increases the ON-evoked EPSCs at a threshold intensity of 60–100 μA for all frequencies. Residual responses remaining in the presence of LY341495 and CNQX, APV, and gabazine were abolished by low $Ca^{2+}$-ACSF, as shown for the single-pulse and 200 Hz stimulation frequencies. $^{*}P < 0.05$, $\#P < 0.001$ vs. CNQX, APV, and gabazine. Modified from M. Ennis *et al*., 2006, J. Neurophysiol. 95, 2233–2241, with permission from The American Physiological Society.



inhibition of glutamate transporters (e.g., TBOA) (Figure 5). Thus, activation of mGluR1 is tightly regulated by glutamate uptake mechanisms. mGluR1-mediated responses were maximal with bursts of 50–100 Hz ON spikes, similar to frequencies of odor-induced spikes in ORNs *in vivo* (Duchamp-Viret, P. *et al.* 1999). Activation of mGluRs has also been suggested to produce long-term depression at ON to mitral cell synapses (Mutoh, H. *et al.*, 2005).

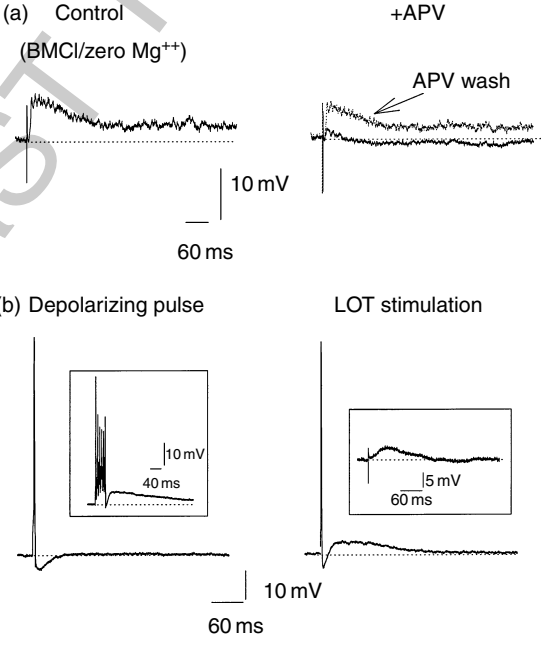
p0070 All ET cells receive monosynaptic ON input, which appears to be primarily mediated by AMPA and NMDA receptors in normal physiological conditions *in vitro* (Figure 4) (Hayar, A. *et al.*, 2004a; 2004b; 2005). If the amplitude of an ON-evoked EPSP reaches threshold for spike generation, a spike burst is always triggered in ET cells (Hayar, A. *et al*, 2004a). Further increases in ON stimulation strength produce the same all-or-none burst. Thus, ET cells receive monosynaptic ON input that is converted into an all-or-none spike burst. Accordingly, ET cells amplify suprathreshold sensory input at the first stage of synaptic transfer in the olfactory system. ET cells also readily entrain to rhythmic ON input delivered at theta frequencies (5–10 Hz) characteristic of investigative sniffing in rodents. As noted above, the intrinsic spontaneous bursting rate of ET cells ranges from 1 to 8 bursts/s. This might suggest that ET cells with different spontaneous bursting rates may be preferentially entrained by repetitive sensory input at or near their intrinsic bursting frequency. This turns out not to be the case as ET cells, irrespective of their intrinsic spontaneous bursting frequencies, can be entrained by repetitive, 5–10 Hz ON input (Hayar, A. *et al.*, 2004a).

p0075 The majority of PG cells exhibit longer latency, prolonged bursts of EPSP/Cs in response to ON stimulation than ET cells (Figure 4). The long, variable latency of these responses is indicative of di- or polysynaptic ON input. 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. Only 20% of PG cells had short, relatively constant latency EPSCs following ON stimulation, and in some of these cells, the short latency synaptic response was followed by a delayed burst of EPSP/Cs. SA cells also responded to ON stimulation with long, variable latency, prolonged bursts of EPSP/Cs and never exhibited responses consistent with monosynaptic ON input (Figure 4). These findings indicate that (1) SA cells and most PG cells lack direct ON input and (2) ET cells along with mitral/tufted cells are the major postsynaptic targets of ON inputs.

p0080 Since most (~80%) PG cells, and all SA cells, lack monosynaptic ON input, this suggests that most PG cells are functionally associated with glomerular compartments lacking 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 of which is devoid of ON input (Kosaka, T. *et al.*, 1997; Kasowski, H. J. *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, K. *et al.*, 1998; 2000). It is reasonable to speculate, therefore, that the SA and PG cells that do not receive direct input (Hayar, A. *et al.*, 2004b) may correspond to these calbindin-positive JG neurons. These PG cells might provide localized inhibition to mitral/tufted cell dendrites, or other nearby JG cells. Dopaminergic and GABAergic PG cells presynaptically inhibit ON terminals (Hsia, A. Y. *et al.*, 1999; Wachowiak, M. and Cohen, L. B., 1999; Aroniadou-Anderjaska, V. *et al.*, 2000; Berkowicz, D. A. and Trombley, P. Q., 2000; Ennis, M. *et al.*, 2001; Murphy, G. J. *et al.*, 2005; Wachowiak, M. *et al.*, 2005). Since at least 20% of PG cells receive monosynaptic ON input, it is possible that these cells primarily mediate this presynaptic inhibition of the ON. In contrast to PG cells, SA cells extend dendrites and axons across multiple glomeruli and are thought to be involved in interglomerular functions, such as center-surround inhibition of neighboring glomeruli (Aungst, J. L. *et al.*, 2003).

s0060 ***2.44.2.2.1.(ii) Spillover of dendritically released glutamate*** p0085 As noted above, the apical dendrites of ET and mitral/tufted cells that ramify in the glomeruli release glutamate. Although the dendrites of these cell types do not form synapses with each other, the release of glutamate from the apical dendrites has been reported to produce nonsynaptically mediated excitation (i.e., glutamate spillover) of the parent cell releasing glutamate (self- or autoexcitation) or neighboring cells (Figure 6). Such excitation is facilitated by removal of $Mg^{2+}$ from the extracellular media, which enhances the activation of NMDA receptors. Alternatively, spillover-mediated excitatory responses can be facilitated in the presence of physiological levels of extracellular $Mg^{2+}$ by blockade of $GABA_A$ receptors (Salin, P. A. *et al.*, 2001; Friedman, D. and Strowbridge, B. W., 2000). Under such conditions, intracellular depolarization of individual mitral cells produces long-duration, NMDA receptor-dependent excitation of the same cell or




f0030 **Figure 6** Mitral cells generate an NMDA receptor-dependent EPSP in response to antidromic stimulation of neighboring mitral/tufted cells. Panels a and b show recordings from two different cells in $Mg^{2+}$-free medium and bicuculline (10 μM). (a) Antidromic activation of mitral/tufted cells by lateral olfactory tract (LOT) stimulation, subthreshold for the recorded neuron, evoked an EPSP that was reversibly blocked by bath-applied APV (50 μM). (b) Mitral cell shown did not produce a prolonged depolarization in response to a 5 ms intracellular current pulse. However, a prolonged depolarization was evoked by longer current pulses (40 ms, shown in inset) or LOT stimulation with or without (inset) an antidromic spike. Traces are averages of five to ten sweeps. Reprinted from V. Aroniadou-Anderjaska *et al.*, 1999, J. Neurophysiol. 82, 489–494, with permission from The American Physiological Society.

adjacent mitral cells (Aroniadou-Anderjaska, V. *et al.*, 1999b; Isaacson, J. S., 1999; Strowbridge, B. W., 2000; Salin, P. A. *et al.*, 2001; Friedman, D. and Christie, J. M. and Westbrook, G. L., 2006). ET cells have also been reported to exhibit such self-excitation (Murphy, G. J. *et al.*, 2005). The mitral cell self-excitation can be blocked by intracellular $Ca^{2+}$ chelation or blockade of voltage-gated $Ca^{2+}$ channels (Friedman, D. and Strowbridge, B. W., 2000; Salin, P. A. *et al.*, 2001). The self-excitation responses are graded and increase with the number of spikes or depolarizing pulses applied to the mitral cell (Friedman, D. and Strowbridge, B. W., 2000; Salin, P. A. *et al.*, 2001). It has been suggested that the NMDA autoreceptors may serve to increase the firing frequency of mitral cells during prolonged discharges (Friedman, D. and Strowbridge, B. W., 2000). Such excitation can also be evoked by antidromic activation of mitral cells (Figure 6) (Chen, W. R. and Shepherd, G. M., 1997; Aroniadou-Anderjaska, V. *et al.*, 1999b). This glutamate spillover-mediated, NMDA receptor-dependent excitation appears to occur chiefly among the lateral dendrites of mitral cells, while an AMPA receptor-dependent spillover occurs among the apical dendrites of mitral/tufted cells (Aroniadou-Anderjaska, V. *et al.*, 1999b; Salin, P. A. *et al.*, 2001; Schoppa, N. E. and Westbrook, G. L., 2001; 2002; Christie, J. M. and Westbrook, G. L., 2006). Electrotonic coupling among mitral cell dendrites in the same glomerulus facilitates spillover responses mediated by AMPA receptors (Schoppa, N. E. and Westbrook, G. L., 2002; Christie, J. M., and Westbrook, G. L., 2006).

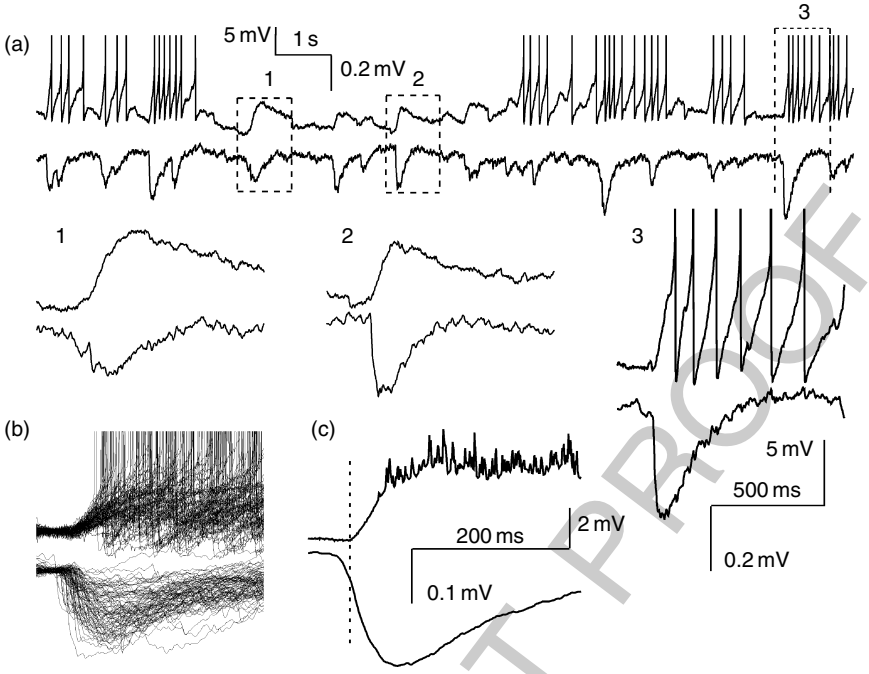
p0090 Other glomerulus-specific glutamate-mediated excitatory interactions among mitral cells have been reported. Reciprocal glutamate-mediated excitation was reported between closely adjacent mitral cells whose apical dendrites extended into the same glomerulus (Urban, N. N. and Sakmann, B., 2002). The latency for the mitral to mitral cell EPSPs was surprisingly short, in line with monosynaptic mediation, despite the fact that mitral cells do not form anatomical synapses with each other. The EPSP was primarily mediated by AMPA receptors and originated within the GL, suggesting that they are generated in the apical dendrites of mitral cells. In contrast to the preceding studies, Carlson G. C. *et al.* (2000) reported that ON stimulation and antidromic activation of multiple mitral/tufted cells, but never activation of single mitral cells, elicited long-lasting depolarizations (LLDs) in mitral cells. The LLDs were all-or-none in nature, required activation of AMPA receptors, and originated in the glomeruli. Further, spontaneous LLDs were synchronous among mitral cells associated with the same, but not different glomeruli. The LLDs appear to be a network phenomenon, presumably reflecting recurrent, intraglomerular glutamate release from an ensemble of mitral/tufted cell apical dendrites. Recently, Karnup S. V. *et al.* (in press) described field potentials that are generated spontaneously in the GL in olfactory bulb slices (Figure 7). These spontaneous glomerular local field potentials (sGLFPs) had variable shape and amplitude and occurred at irregular intervals. They are similar to LLDs in mitral cells (Carlson, G. C. *et al.*, 2000) in that they are mediated mostly by AMPA/kainate receptors and are enhanced during blockade of $GABA_A$ receptors. They persisted after the removal of the MCL, indicating that they are predominantly generated from by GL neurons. Nevertheless, they were correlated with mitral cell postsynaptic LLDs, suggesting the existence of a common generator (Figure 7). The observation that sGLFPs precede LLDs in mitral cells suggests that mitral cells are followers rather than initiators of population events. The most likely scenario is that mitral cells are activated when a critical number of glutamate-releasing JG neurons (presumably ET cells) are activated. Such a triggering mechanism may be produced by synchronous spike bursts in ET cells of the same glomerulus (Hayar, A. *et al.*, 2004a; 2004b). The role of spillover-mediated excitation among mitral/tufted cells is discussed below in Synchrony.

***2.44.2.2.1.(iii) ET and mitral/tufted cell dendrodendritic input to PG and SA cells*** s0065 p0095 ET and mitral/tufted cells form glutamatergic dendrodendritic synapses with PG and SA cells. This topic is discussed below in *ET and mitral/tufted cell dendrodendritic interactions with PG and SA cells.*

### *2.44.2.2.2 Inhibitory systems in the GL* s0070

#### *2.44.2.2.2.(i) Presynaptic inhibition of ON terminals* s0075

***2.44.2.2.2.(i).(a) DA and D2 receptors*** s0080 p0100 The GL contains several hundred thousand DA neurons – PG neurons – but the MOB receives no known extrinsic DA input. In mammals, D1 receptor mRNA is expressed in the GL and GCL (Coronas, V. *et al.*, 1997), while immunocytochemical localization of D1 receptors is faint and primarily in the GCL (Levey, A. I. *et al.*, 1993). By contrast, D1-like binding is present at very low levels in all layers of the MOB

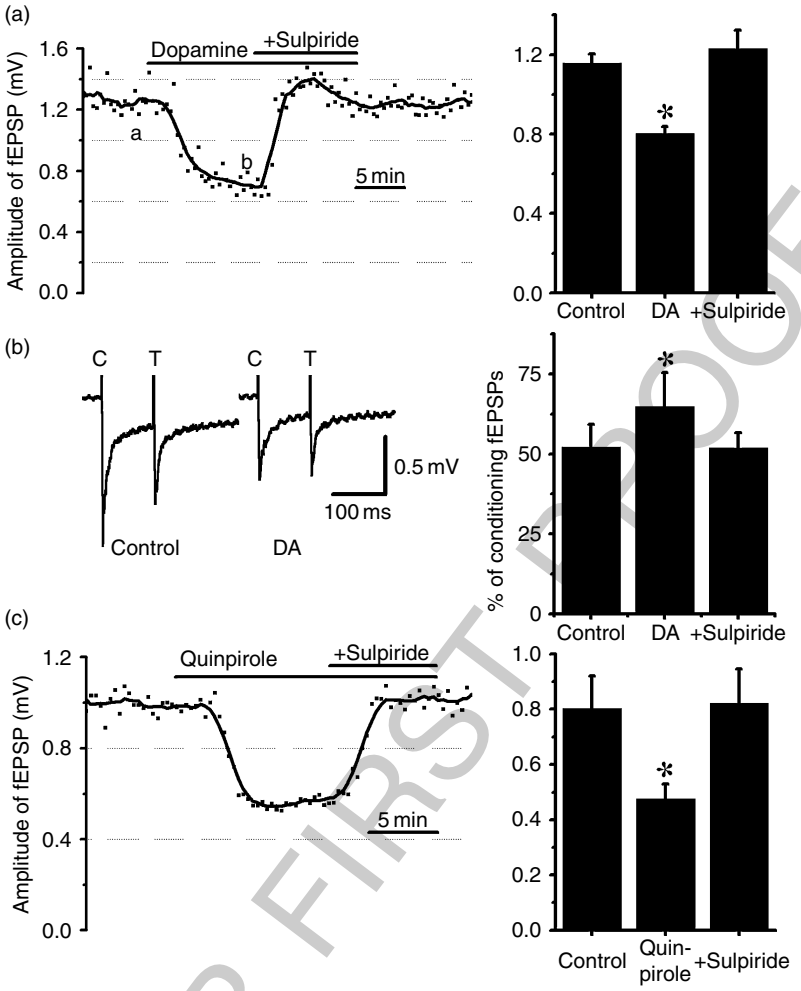



f0035 **Figure 7** Glomerular and mitral cell long-lasting depolarizations (LLDs). Simultaneous recordings of spontaneous LLDs (sLLDs) in a mitral cell and spontaneous glomerular layer field potentials (sGLFPs) from the glomerulus containing the mitral cell tuft. (a) Dual sweep of intracellular (upper trace) and field activity (lower trace). Spikes of the mitral cell are truncated. Insets with an expanded timescale demonstrate variability of sGLFP locked to sLLD and different kinetics of sGLFP as compared with sLLD. (b) Overlapping sweeps with sLLD/sGLFP pairs ($n = 80$). Note 10-fold difference between smallest and biggest sGLFP indicating different amount of cells involved in successive sGLFP in a given glomerulus. (c) Averaged sLLD and sGLFP ($n = 80$) with the reference point set at the sLLD onset show 9.8 ms delay of sLLD upon initiation of sGLFP.



with the exception of the ONL (Mansour, A. *et al.*, 1990; Nickell, W. T. *et al.*, 1991; Coronas, V. *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, A. *et al.*, 1990; Nickell, W. T. *et al.*, 1991; Levey, A. I. *et al.*, 1993; Coronas, V. *et al.*, 1997; Koster, N. L. *et al.*, 1999) and to a lesser extent in guinea pigs, but not in cats or monkeys (Camps, M. *et al.*, 1990). In the GL, the JG neurons express D2 receptors (Mansour, A. *et al.*, 1990). 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, A. *et al.*, 1990; Levey, A. I. *et al.*, 1993; Coronas, V. *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 AU14 mRNA in the olfactory epithelium (Koster, N. L. *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 ago- p0105 nists reduced spontaneous and ON-evoked activity in mitral and JC cells (Figure 8), as well as odor-evoked activity in the GL and odor detection performance, in a variety of species (Nowycky, M. C. *et al.*, 1983; Doty, R. L. and Risser, J. M., 1989; Sallaz, M. and Jourdan, F., 1992; Hsia, A. Y. *et al.*, 1999; Wachowiak, M. and Cohen, L. B., 1999; Berkowicz, D. A. and Trombley, P. Q., 2000; Ennis, M. *et al.*, 2001). These effects are mediated by presynaptic suppression of glutamate release from ON terminals via inhibition of $Ca^{2+}$ influx (Wachowiak, M. and Cohen, L. B., 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, M. *et al.*, 2001). The inhibitory effects of DA were abolished in D2 receptor-knockout mice (Ennis, M. *et al.*, 2001). Presynaptic



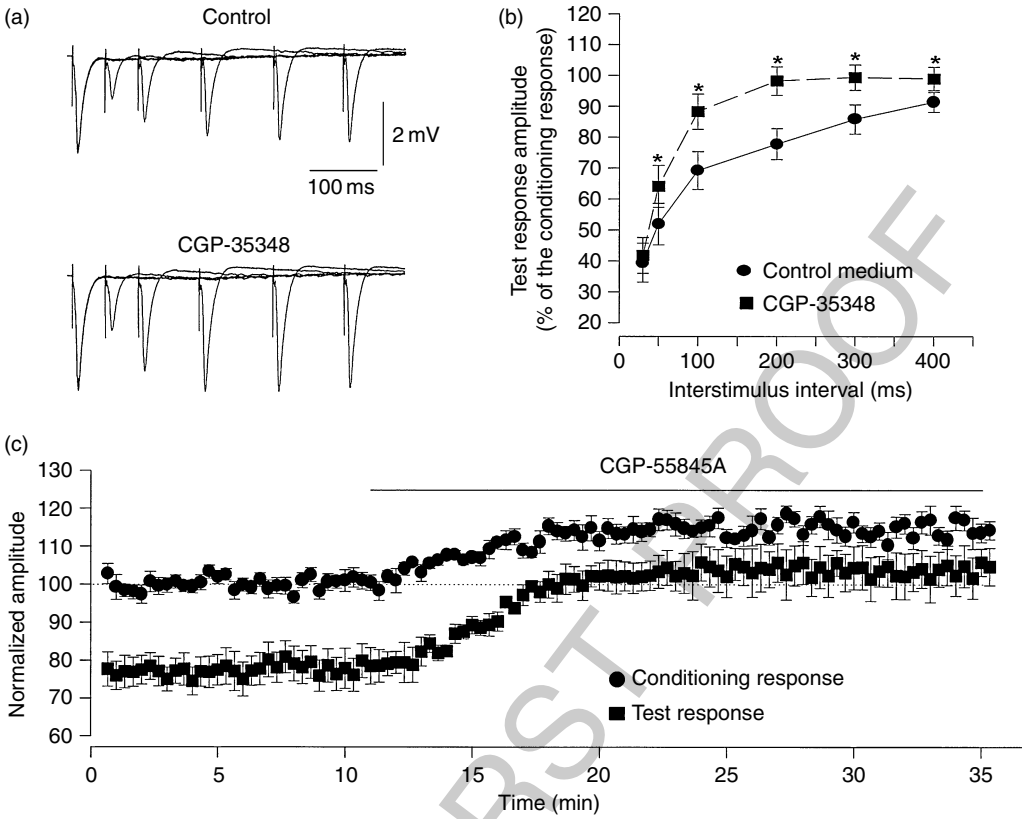

f0040 **Figure 8** Dopamine (DA) suppresses the olfactory nerve (ON)-evoked field excitatory postsynaptic potential (fEPSP) recorded in the rat glomerular layer (GL). (a) Line graph from a typical experiment showing the suppression of the GL fEPSP by bath application of DA (40 μM). Values represent the peak amplitude ± SE of the fEPSP. DA-induced suppression (30.7%) was fully reversed by the D2 antagonist sulpiride (100 μM). Group data at the right from similar experiments show that DA significantly suppresses ($n = 5$, $^*P = 0.005$) the ON-evoked fEPSP, an effect fully reversed by sulpiride ($n = 4$). (b) Records show responses to paired-pulse stimulation of the ON (100-ms interstimulus intervals) before (Control) and during application of DA (DA); control and DA records correspond to time points a and b indicated in panel a. In control artificial cerebrospinal fluid (ACSF), paired ON shocks produced pronounced paired-pulse depression of the test fEPSP. DA preferentially suppressed the conditioning shock fEPSP and decreased paired-pulse depression. Traces are averages of five sweeps. Bar graph of group data showing the change in paired-pulse responses to ON stimulation; data are expressed as the amplitude of the test fEPSP as a percentage of the conditioning fEPSP. Note that DA significantly reduced paired-pulse depression ($n = 4$, $^*P = 0.01$). (c) Line graph showing the suppression of the GL fEPSP by bath application of quinpirole (100 μM). Sulpiride (100 μM) fully reversed the quinpirole-induced suppression. Group data for similar experiments are shown in the bar graphs to the right ($n = 10$, $^*P < 0.0001$). Reprinted from M. Ennis *et al.*, 2001, J. Neurophysiol. 86, 2986–2997, with permission from The American Physiological Society.

inhibition of ON terminals by DA (and GABA, see below) provides a mechanism for increasing the range of concentrations that can be processed by MOB neurons: as activity increases in ON terminals, DA JG cells are more strongly excited. This, in turn, provides negative feedback onto 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, R. L. and Risser, J. M., 1989; Sallaz, M. and Jourdan, F., 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 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, D. A. and Sullivan, R. M., 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.

s0085 p0110 ***2.44.2.2.2.(i).(b) GABA and $GABA_B$ receptors*** $GABA_B$ receptors play a presynaptic inhibitory role similar to that just described for D2 receptors. As noted above, 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, N. G. *et al.*, 1987; Chu, D. C. M. *et al.*, 1990) and by immunohistochemical localization of $GABA_B$ receptor subunits (Margeta-Mitrovic, M. *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 on the somata of PG cells (Bonino, M. *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 (Figure 9) (Keller, A. *et al.*, 1998; Wachowiak, M. and Cohen, L. B., 1999; Aroniadou-Anderjaska, V. *et al.*, 2000; Palouzier-Paulignan, B. *et al.*, 2002; Murphy, G. J. *et al.*, 2005). The presynaptic inhibition of glutamate release is mediated by the suppression of $Ca^{2+}$ influx into ON terminals (Wachowiak, M. *et al.*, 2005). Stimulation of individual PG cells has been reported to inhibit, via $GABA_B$ receptors, ON input onto the stimulated cell (Murphy, G. J. *et al.*, 2005). The MOB also contains the highest levels of the putative inhibitory transmitter taurine, exceeding concentrations of GABA and glutamate (Collins, G. G., 1974; Margolis, F. L., 1974; Banay-Schwartz, M. *et al.*, 1989a; 1989b; Ross, C. D. *et al.*, 1995; Kamisaki, Y. *et al.*, 1996). Taurine is found in ON axons, in various neurons, and in astrocytes (Kratskin, I. L. *et al.*, 2000; Kratskin, I. and Belluzzi, O., 2002; Pow, D. V. *et al.*, 2002). In the ON terminals and some postsynaptic dendrites, taurine is colocalized with glutamate (Didier, A. *et al.*, 1994). Observation of spontaneous taurine release from MOB synaptosomes suggests that taurine may be abundantly released (Kamisaki, Y. *et al.*, 1996). In electrophysiological recordings, taurine directly activated presynaptic $GABA_B$ receptors and inhibited ON terminals, and it also induced $Cl^-$ currents in mitral/tufted cells. Surprisingly, taurine had no direct effect on PG cells (Belluzzi, O. *et al.*, 2004).

s0090 p0115 ***2.44.2.2.2.(i).(c) ET and mitral/tufted cell dendrodendritic interactions with PG and SA cells*** As noted above, ET and mitral/tufted cells form excitatory glutamatergic dendrodendritic synapses with PG and SA cells in the glomeruli. PG cells, and perhaps SA cells, in turn, form inhibitory GABAergic dendrodendritic synapses with ET and mitral/tufted cells. Although the ET and mitral/tufted cell input is excitatory, this topic is considered here for simplicity. Compared to the dendrodendritic synapses between mitral/tufted and GCs in the EPL, far less is known about the properties of the dendrodendritic synapses in the GL. PG and SA cells were reported to receive spontaneous bursts of glutamatergic EPSCs (Hayar, A. *et al.*, 2004b). Since SA cells and most PG cells do not receive direct ON input, this input must arise from other excitatory elements within the glomeruli. Prime candidates include the apical dendrites of ET cells and mitral tufted cells. Consistent with this, stimulation of the MCL or lateral olfactory tract (LOT) has been used to produce antidromic spikes which would propagate into, and trigger glutamate release from, mitral/tufted cell apical dendrites. Such stimulation was reported to excite JG cells in the GL (Ennis, M. *et al.*, 2001). More recently, spontaneous spike bursts or direct depolarization of individual ET cells to elicit spike bursts were reported to trigger EPSC bursts in PG and SA cells mediated by activation of AMPA receptors (Figure 10) (Hayar, A. *et al.*, 2004b). The latency of the evoked EPSCs (0.85 ms) was indicative of monosynaptic input to PG cells from ET cells. Additional studies demonstrated that this ET cell to PG/SA cell excitatory transmission is intraglomerular as it was only observed between cells associated with the same glomerulus. Stimulation of an individual ET cell was reported to produce large EPSCs and $Ca^{2+}$ spikes in PG cells (Murphy, G. J. *et al.*,

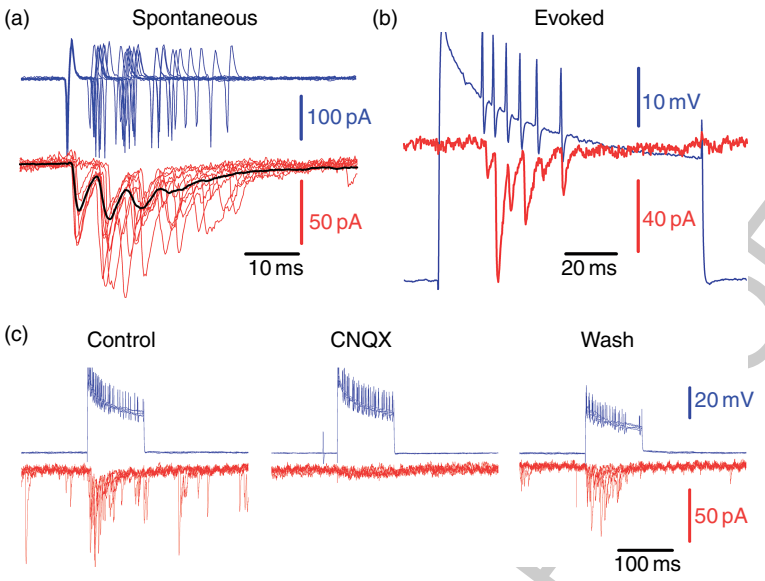



f0045 **Figure 9** GABAB receptors on olfactory nerve (ON )terminals are activated both tonically and in response to ON stimulation. GABAB antagonists increase both conditioning and test responses of mitral/tufted cells to paired-pulse stimulation of the ON, AU15 while reducing PPD of test responses. In all experiments, AP5 is included in the medium. (a) Responses to paired-pulse stimulation of the ON (interstimulus intervals 50, 100, 200, 300, and 400 ms) before and after application of the GABAB antagonist CGP-35348 (1 mM). The GABAB antagonist increased the amplitude of the conditioning response and reduced or blocked PPD. Each trace is an average of five sweeps, and five traces are superimposed. (b) Group data ($n = 10$) of the effects of CGP-35348 (500 μM to 1 mM) on PPD of the ON-evoked glomerular field EPSP. The reduction of PPD was statistically significant ($^*P < 0.05$) at interstimulus intervals from 50 to 400 ms. (c) Time course of the effects of CGP-55845A (10 μM) on conditioning and test responses (interstimulus interval 100 ms). Group data from six slices. Reprinted from Aroniadou-Anderjaska, V. *et al*., 2000, J. Neurophysiol. 84, 1194–1203, with permission from The American Physiological Society.

AU16 2005). The NMDA receptor antagonist APV had minimal effects on the EPSP but abolished the $Ca^{2+}$ spike. The same study reported that stimulation of a single ET cell excites two to seven unidentified JG cells within the same glomerulus, suggesting that individual ET cells synapse with multiple PG cells.

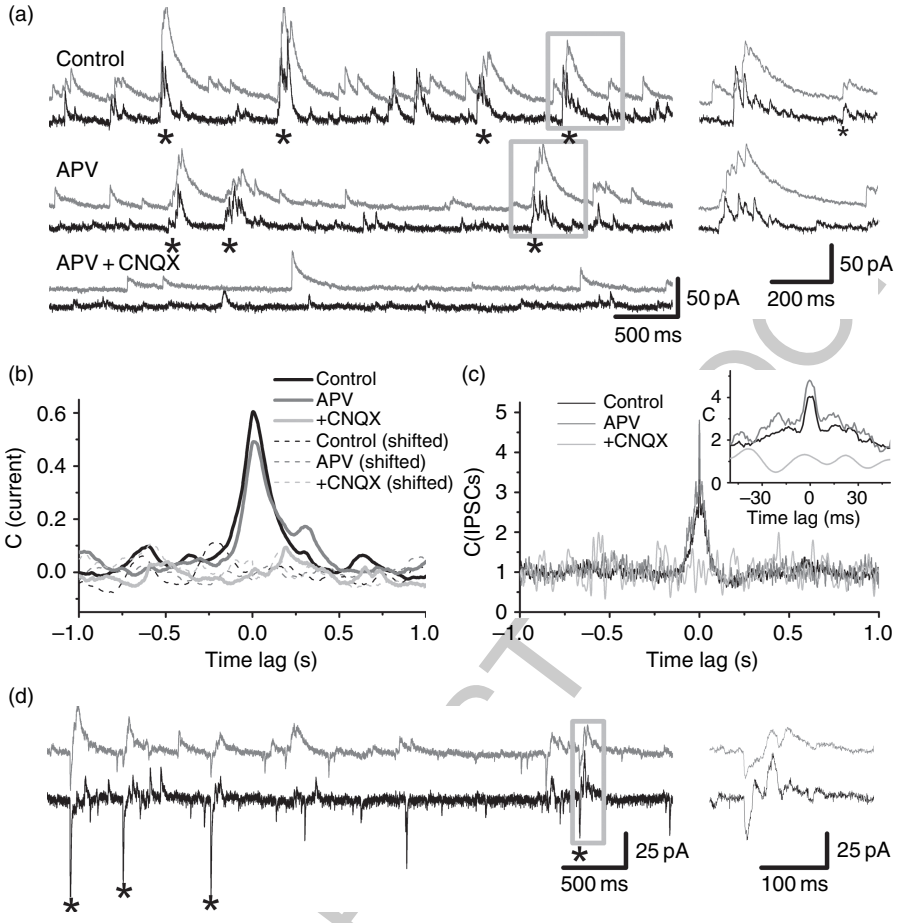
p0120 Single spikes in ET cells are relatively ineffective in triggering GABA release from PG cells (Murphy, G. J. *et al*., 2005). Multiple spikes, leading to LVA $Ca^{2+}$ currents, are much more effective in releasing GABA from PG cells (Murphy, G. J. *et al*., 2005). These findings suggest that GABA release from PG cells may be preferentially triggered when these cells receive strong synaptic input. ET cells, individually and collectively, provide strong input to PG cells. Spike bursts in individual ET cells robustly activate PG cells. Additionally, individual ET cells appear to activate, on average, five PG cells (Murphy, G. J. *et al*., 2005). Since ET cells spontaneously generate synchronous spike bursts and provide convergent input to a multiple PG cells, they are likely to drive tonic release of GABA from PG cells. By contrast, dendrodendritic input from mitral cells, which do not spontaneously burst *in vitro*, may play a larger role in driving GABA release following sensory input.

PG cells contain GABA, and thus activation of p0125 these cells will cause dendrodendritic inhibition of ET and mitral/tufted cell dendrites in the glomeruli. In the PG spaces, their axons also form symmetrical synapses onto the mitral/tufted cell dendrites and




f0050 **Figure 10** External tufted (ET) cells provide monoexcitatory synaptic input to periglomerular (PG) and short axon (SA) cells. (a) Dual recordings from an ET cell in cell-attached mode (blue traces) and a PG/SA cell in whole-cell voltage-clamp mode (red traces). Left panel (Spontaneous) shows 10 superimposed spontaneous spike burst-triggered traces (triggered on the first spike in the burst); black line is the average of 135 similar traces. Note that spontaneous action currents (blue trace) are accompanied by phase-locked busts of EPSCs (red trace). (b) (Evoked) shows an example of a burst of EPSCs (red trace) evoked by a burst of spikes elicited by extracellular injection of a positive current pulse (700 pA, 100 ms). Note close correspondence between evoked spikes in the ET cell and EPSCs in the SA/PG cell. (d) Recordings from the same two cells shown in panels a and b before (Control), during, and after (Wash) application of CNQX (10 μM). Note that bursts of EPSCs (red traces) in the SA/PG cell elicited by current injection-evoked spikes (blue traces) in the ET cell are completely blocked by CNQX (middle) in a reversible manner (right). CNQX also reversibly abolished spontaneous EPSCs. All panels show five superimposed sweeps. Modified from Hayar, A. *et al*., 2004, J. Neurosci. 24, 6676–6685, with permission from The Society for Neuroscience.

onto PG and SA cells (Pinching, A. J. and Powell, T. P., 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 cells (Shepherd, G. M. and Greer, C. A., 1998; Hayar, A. *et al*., 2004b). Such inhibition is thought to be primarily mediated by $GABA_A$ receptors. ET cells exhibit spontaneous bursts of IPSCs, indicating that these are tonically inhibited by GABAergic inputs (Figure 11) (Hayar, A. *et al*., 2005). Spontaneous or ON-evoked EPSCs in ET cells are followed by bursts of IPSCs that are synchronous among ET cells of the same glomerulus. Thus, inhibitory GABAergic input from PG cells may coordinate the activity of ET cells associated with the same glomerulus. Intracellular depolarization of ET cells leads to GABAergic inhibition due to activation of dendrodendritic synapses with PG cells (Murphy, G. J. *et al*., 2005). Using this paradigm, the feedback inhibition produced by ET cell depolarization was reduced by nimodopine, a blocker of L-type $Ca^{2+}$ channels; nimodipine, however, did not reduce GABA release from PG cells. Subsequent experiments, using paired recordings of PG cells, suggested that GABA exocytosis from these cells is governed primarily by activation of HVA, P/Q-type $Ca^{2+}$ channels. The L-type antagonist nimodipine did not directly alter GABA exocytosis from PG cells, leading to the conclusion that activation of LVA currents can facilitate GABA release from PG cells, but these channels are not directly coupled to GABA exocytosis. These studies and others (Smith, T. C. and Jahr, C. E., 2002) also indicate that PG cells, under certain circumstances, can release GABA onto themselves, and perhaps neighboring PG cells. GABA has been reported to depolarize PG cells at their resting potential, probably due to elevated intracellular chloride concentrations (Siklos, L. *et al*., 1995; Smith, T. C. and Jahr, C. E., 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




f0055 **Figure 11** Synchronous bursts of IPSCs in external tufted (ET) cell pairs. All data in this figure were obtained from the same ET cell pair. (a) Simultaneous whole-cell voltage-clamp recordings (holding potential = 0 mV) from two ET cells (gray and black traces, respectively) show synchronous IPSC bursts (asterisks) before and during application of AP5 (50 μM). Note that although AP5 reduced burst frequency, bursts remained synchronous in the two cells. Additional application of CNQX eliminated the IPSC burst synchrony. Areas highlighted in rectangles are shown at faster timescale at right. (b) Membrane current cross-correlograms (50 s recording samples, 2 ms bins) in control, APV, and after additional application of CNQX. Note the significant peak at zero lag time in control and APV. There was no significant correlation after application of CNQX. The 99.73% confidence limit was determined by cross-correlating traces shifted by 5 s (dashed traces). (c) Cross-correlogram of the IPSC trains (5 min recording samples, 1 ms bins) show a significant narrow peak (see inset) at zero time lag, indicating synchronous IPSCs in the two recorded cells. The narrow peak was superimposed on a broader peak corresponding to the longer duration correlated IPSC bursts. CNQX abolished correlation and synchrony of IPSCs. (d) Simultaneous whole-cell voltage-clamp recordings (holding potential = − 30 mV) from the same two ET cells showing synchronous EPSCs followed by IPSC bursts; recording highlighted in rectangle is shown at faster timescale at right. Recordings obtained before the application of synaptic blockers (CNQX, AP5, gabazine) in (a). Modified from Hayar, A. *et al*., 2005, J. Neurosci. 25, 8197–8208, with permission from The Society for Neuroscience.

cells in the same glomerulus via GABAA receptors (Murphy, G. J. *et al*., 2005). Because PG cell dendrites ramify within a restricted portion of a glomerulus, their functional interactions are presumably localized to microdomains of the extensive mitral/tufted cell dendritic arbors, or to nearby JG cells (Kasowski, H. J. *et al*., 1999).

***2.44.2.2.2.(ii) Neuromodulation in the GL*** s0095

p0130 Neuromodulatory systems in the GL include carnosine and certain heavy metals (copper and zinc), and neuromodulatory inputs from centrifugal afferents. Centrifugal inputs are discussed below (see Neurophysiology of Neuromodulatory Inputs to Main Olfactory Bulb). Carnosine, a dipeptide

synthesized by ORNs, is localized in ON terminals in the GL and fulfills many criteria for neurotransmitter candidacy. However, no direct postsynaptic actions of carnosine have been revealed to date (MacLeod, N. K. and Straughan, D. W., 1979; Nicoll, R. A. and Alger, B. E., 1980; Frosch, M. P. and Dichter, M. A., 1982; Trombley, P. Q. *et al.*, 1998). Carnosine did not affect currents evoked by glutamate, GABA, or glycine in cultured MOB neurons (Trombley, P. Q. *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 AU17 currents and synaptic transmission in MOB neurons (Trombley, P. Q. and Shepherd, G. M., 1996; Trombley, P. Q. *et al.*, 1998). Carnosine prevented the actions of copper and reduced the effects 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, M. S. *et al.*, 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.

s0100 #### 2.44.2.3 Electrophysiology of Interglomerular Circuitry

p0135 Interglomerular interactions are poorly understood. As noted above, SA cells frequently have multiple dendrites (three to five) that extend over several (two to four) glomeruli (Aungst, J. L. *et al.*, 2003). Thus, these cells may receive odor information from multiple glomeruli. These cells do not receive direct ON input, but instead appear to receive olfactory input indirectly from ET and mitral/tufted cells (Hayar, A. *et al.*, 2004b). In turn, SA cells give rise to an axon that extends for considerable distances (~0.85 mm) in the GL (Aungst, J. L. *et al.*, 2003). Imaging studies suggest that the SA cells may be involved in lateral inhibition between glomeruli. Stimulation of the GL was reported to produce monosynaptic excitation of most ET and PG cells neurons in neighboring glomeruli mediated by activation of ionotropic glutamate receptors (Aungst, J. L. *et al.*, 2003). This suggests the intriguing possibility that SA cells are excitatory. Further, a prepulse to one glomerulus inhibited ON-evoked excitation of mitral cells in another glomerulus. It was concluded that the net functional effect of SA cell activation is to excite PG cells in other glomeruli, causing the release of GABA and inhibition of mitral cell responses to ON input. Taken together, these findings suggest that SA cells represent a major neural element for interglomerular interactions and that these cells may provide a substrate for center-surround inhibition – a common mechanism to enhance stimulus contrast in sensory circuits.

## 2.44.3 Neurophysiology of External Plexiform Layer s0105

### 2.44.3.1 Tufted Cells s0110

p0140 Tufted cells are the most numerous cells of the EPL. Three subclasses of tufted cells are recognized based on location in the EPL: superficial, middle, and deep tufted cells (Cajal, R. S. Y., 1890; Pinching, A. J. and Powell, T. P., 1971a; Macrides, F. and Schneider, S. P., 1982; Orona, E. *et al.*, 1984). Like ET cells and mitral cells, tufted cells of the mammalian EPL have one (or rarely several) apical dendrite(s) ending in a glomerular tuft (Cajal, R. S. Y., 1890). Like mitral cells, their apical dendrites receive ON input, and they form reciprocal dendrodendritic synapses with the dendrites of PG and SA cells. Their lateral dendrites ramify in the EPL and form dendrodendritic synapses with GCs and other inhibitory interneurons within the EPL. The neurophysiology of dendrodendritic interactions between mitral/tufted cells and GCs in the EPL is discussed below. Axonal projections of middle and deep tufted cells are similar, but not identical, to those of mitral cells (Schoenfeld, T. A. and Macrides, F., 1984; Schoenfeld, T. A. *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 anterior olfactory nucleus and, to a lesser extent, in other rostral olfactory cortical structures (Schoenfeld, T. A.

*et al.*, 1985; Scott, J. W., 1986). Few tufted cell axons project into more caudal POC regions.

p0145 Tufted cells utilize glutamate as their principle transmitter (Liu, C. J. *et al.*, 1989; Christie, J. M. *et al.*, 2001), but they also stain for a number of other AU18 substances, including CCK. *In vivo* electrophysiological recordings have shown that the sensitivity of tufted 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 (Schneider, S. P. and Scott, J. W., 1983; Wellis, D. P. *et al.*, 1989; Ezeh, P. I. *et al.*, 1993). In response to odor stimulation, superficially located tufted cells also exhibit more prolonged excitation than mitral cells (Luo, M. and Katz, L., 2001). More recent studies have reported that tufted cells can be excited for up to several minutes following odorant presentation (Luo, M. and Katz, L., 2001). Thus, anatomically distinct tufted cell subtypes appear to be functionally distinct. In slices, tufted cells have been observed to exhibit spontaneous and ON-evoked bursting activity somewhat similar to that of ET cells (Hamilton, K. A. *et al.*, 2005). The extent to which such bursting varies among different tufted cell subtypes, as well as the mechanisms generating bursting, is unknown.

p0150 Many superficial tufted cells contain CCK (Seroogy, K. B. *et al.*, 1985), and their axons give rise to a reciprocal network, the intrabulbar association system (IAS) that connects lateral and medial regions of each MOB (Schoenfeld, T. A. *et al.*, 1985). The axons of the IAS 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, W. L. and Shipley, M. T., 1994). The IAS projection exhibits a high degree of point-to-point specificity. The IAS projections from tufted cells associated with a single glomerulus preferentially target the IPL deep to the second glomerulus on the other side of MOB (Belluscio, L. *et al.*, 2002; Lodovichi, C. *et al.*, 2003). 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. CCK typically is excitatory, and therefore the IAS may depolarize GCs.

#### s0115 2.44.3.2 EPL Interneurons

p0155 The EPL contains anatomically and neurochemically heterogeneous subtypes of intrinsic interneurons (for review, see Ennis, M. *et al.*, in press). Many EPL interneurons stain for GABA and are therefore presumed to be inhibitory (Mugniani *et al.*, 1984a; AU19 Gall, C. M. *et al.*, 1987; Kosaka, T. *et al.*, 1987d; Ohm, T. G. *et al.*, 1990). EPL interneuron subtypes are neurochemically diverse and stain for a number of neurotransmitter markers, including NADPH diaphorase (Scott, J. W. *et al.*, 1987; Villalba, R. M. *et al.*, 1989; Alonso, J. R. *et al.*, 1995), substance P (Baker, H., 1986; Wahle, P. *et al.*, 1990), enkephalin (Bogan, N. *et al.*, 1982; Davis, B. J. *et al.*, 1982), NPY (Gall, C. *et al.*, 1986; Scott, J. W. *et al.*, 1987; Sanides-Kohlrausch, C. and Wahle, P., 1990a), neurotensin and somatostatin (Matsutani, S. *et al.*, 1988), and VIP (Gall, C. *et al.*, 1986; López-Mascaraque, L. *et al.*, 1989; Sanides-Kohlrausch, C. and Wahle, P., 1990b; Nakajima, T. *et al.*, 1996). The role of these transmitters in the function of EPL interneurons is not known. EPL interneurons are thought to interact chiefly with mitral/tufted cell dendrites (López-Mascaraque, L. *et al.*, 1990; Nagayama, S. *et al.*, 2004) and possibly GC dendrites (Schneider, S. P. and Macrides, F., 1978). Combined morphological and electrophysiological analyses showed that GABAergic EPL interneurons with highly varicose dendrites are excited polysynaptically by ON stimulation, most likely via input from nearby mitral/tufted cells (Hamilton, K. A. *et al.*, 2005). The interneurons exhibit high levels of spontaneous glutamatergic synaptic activity mediated by AMPA/kainate receptors, consistent with GluR1 AMPA receptor subunit staining in these cells (Petralia, R. S. and Wenthold, R. J., 1992; Giustetto, M. *et al.*, 1997; Montague, A. A. and Greer, C. A., 1999; Hamilton, K. A. and Coppola, D. M., 2003). Many EPL interneurons have dendrites that spanned several adjacent glomeruli, suggesting that they may provide localized inhibition of mitral/tufted cells that are topographically related to overlying glomeruli (Hamilton, K. A. *et al.*, 2005).

### 2.44.4 Neurophysiology of Mitral Cells s0120

#### 2.44.4.1 Anatomical Features s0125

p0160 Deep to the EPL is the MCL, a thin layer that contains the somata of mitral cells as well as numerous GCs (Cajal, R. S. Y., 1911a; 1911b). In fact, there are ~40,000 mitral cells (Meisami, E., 1989) and ~100,000 GCs in the MCL (Frazier, L. L. and Brunjes, P. C., 1988). Thus, mitral cells comprise less than one-half of the cells in the MCL. Together with tufted cells, mitral cells are the major class of output cells of the bulb. As noted above, mitral cells extend a single apical dendrite into

one glomerulus. There are about 25 mitral cells (and 50 tufted cells) associated with a single glomerulus (Cajal, R. S. Y., 1911a; 1911b; Allison, A., 1953). The apical dendrites are synaptically contacted by ON terminals (Price, J. L. and Powell, T. P. S., 1970a; Shepherd, G. M., 1972). The secondary or lateral dendrites of mitral cells ramify in the EPL where they may extend up to 1–2 mm. These lateral dendrites participate in dendrodendritic synapses with dendrites of GCs, as reviewed below (see Dendrodendritic Transmission Between Mitral/Tufted Cells and Granule Cells). Mitral cells have been subdivided into two classes, Type I and Type II, based on extension of dendrites into the deep or superficial parts of the EPL, respectively (Orona, E. *et al.*, 1984). Type II mitral cells are more easily by ON stimulation than AU20 Type I mitral cells (Schneider, S. P. and Scott, J. W., 1983; Wellis, D. P. *et al.*, 1989; Ezeh, P. I. *et al.*, 1993). Mitral cell lateral dendrites receive centrifugal axon inputs and inputs from EPL interneurons (Jackowski, A. *et al.*, 1978; Toida, K. *et al.*, 1996). Mitral cells give off axon collaterals, which terminate within the bulb, in the IPL and GCL (Price, J. L. and Powell, T. P. S., 1970c; Mori, K. *et al.*, 1983), or exit the MOB and innervate a number of olfactory-related brain regions collectively known as the POC. Mitral (and tufted) AU21 cells are glutamatergic, and the neuropeptide CRF has been demonstrated in mitral and some tufted cells. Substance P has been detected in approximately one-half of mitral cells by in situ hybridization (Warden, M. K. and Young, W. S., 1988), but they do not stain for substance P immunocytochemistry (Inagaki, S. *et al.*, 1982; Shults, C. W. *et al.*, 1984; Baker, H., 1986).

s0130 ### 2.44.4.2 Spontaneous Discharge and Intrinsic Membrane Properties

p0165 *In vivo* extracellular recording studies in anesthetized animals indicate that most mitral cells fire at fairly high spontaneous rates (6–30 Hz; mean rate, ~18 Hz) (Chaput, M. and Holley, A., 1979; Chaput, M., 1983; Yu, G.-Z. *et al.*, 1993; Jiang, M. R. *et al.*, 1996). They also exhibit periodic, long-duration (several minutes) tonic increases and decreases in firing rates that may be related to anesthesia (Yu, G.-Z. *et al.*, 1993; Jiang, M. R. *et al.*, 1996); mitral cells are less responsive to ON during the periods of reduced spontaneous activity. In awake rats, mitral cells firing AU22 rats range from 1 to 33 Hz with a mean rate of 12 Hz (Kay, L. M. and Laurent, G., 1999). A detailed consideration of mitral cell odor responses, receptive fields, and plasticity is beyond the scope of this chapter, and readers are referred to recent work in this area (Kashiwadani, H. *et al.*, 1999; Kay, L. M. and Laurent, G., 1999; Luo, M. and Katz, L., 2001; Fletcher, M. L. and Wilson, D. A., 2003; Nagayama, S. *et al.*, 2004; Mori, K. *et al.*, 2006).

p0170 Mitral cell spontaneous firing patterns and odor responses *in vivo* are modulated as a function of the respiratory cycle. Recent patch clamping studies in anesthetized rodents has provided new information on properties of mitral spontaneous and odor-evoked discharge. Mitral cells exhibit subthreshold membrane potential oscillations or action potentials synchronized to or modulated by respiration, which occurs in the theta frequency range, 1–12 Hz (Philpot, B. D. *et al.*, 1997; Chalansonnet, M. and Chaput, M. A., 1998; Kay, L. M. and Laurent, G., 1999; Charpak, S. *et al.*, 2001; Luo, M. and Katz, L., 2001; Debarbieux, F. *et al.*, 2003; Margrie, T. W. and Schaefer, A. T., 2003). The peak depolarization of the membrane potential oscillation coincides with the peak of the inhalation phase (Margrie, T. W. and Schaefer, A. T., 2003). The rhythmic membrane potential oscillations are blocked by glutamate receptor antagonists, demonstrating that they are synaptically mediated (Margrie, T. W. and Schaefer, A. T., 2003). Combined intrinsic imaging AU23 of glomerular odor responses and intracellular recordings from mitral cells suggests that mitral cell recorded below odor responsive glomeruli are excited by the odor, whereas those cells distant from the activated glomeruli show no response or are inhibited (Luo, M. and Katz, L., 2001). In AU24 responses to excitatory odors, mitral cells typically generate EPSPs and spikes that are synchronized to the inspiratory phase of respiration which occurs in the theta frequency range (Charpak, S. *et al.*, 2001; Margrie, T. W. *et al.*, 2001; Cang, J. and Isaacson, J. S., 2003; Debarbieux, F. *et al.*, 2003; Margrie, T. W. and Schaefer, A. T., 2003). EPSP amplitudes vary proportionately with the strength of the odor stimulus, and spikes are often launched from the rising phase of odor-evoked EPSPs (Cang, J. and Isaacson, J. S., 2003; Margrie, T. W. and Schaefer, A. T., 2003). The latency of the first spike following odor stimuli is inversely proportional to the number of spikes per respiratory cycle such that shorter latencies are observed when spike bursts are elicited (Cang, J. and Isaacson, J. S., 2003; Margrie, T. W. and Schaefer, A. T., 2003). This suggests that the initial spike latency may provide information about the strength of sensory input; i.e., the concentration of

odors. Sufficiently strong odor stimulation triggers a spike burst, with spikes in the burst occurring within the $\beta$–$\gamma$ frequency range (20–60 Hz) (Debarbieux, F. *et al.*, 2003). The interburst spike frequency is constant across bursts that vary in the number of spikes (Margrie, T. W. and Schaefer, A. T., 2003). This suggests that the instantaneous spike frequency probably is not modulated by network-driven factors. Mitral cells also exhibit inhibitory responses to odors (Luo, M. and Katz, L., 2001; Margrie, T. W. *et al.*, 2001; Cang, J. and Isaacson, J. S., 2003). The AU25 strength of odor-evoked IPSPs does not vary with the concentration of the odor stimulus (Cang, J. and Isaacson, J. S., 2003). However, the IPSP amplitudes are larger during the initial respiratory cycle compared to subsequent cycles in the presence of an odorant.

p0175 In slices, mitral cell spontaneous discharge is more modest (1–6 Hz, mean, 3 Hz), presumably because tonic sensory input is absent (Ennis, M. *et al.*, 1996, Ciombor, K. J. *et al.*, 1999; Heyward, P. M. *et al.*, 2001). Mitral cell spontaneous firing is intrinsically generated and persists in the presence of blockers of ionotropic glutamate and GABA receptor antagonists (Ennis, M. *et al.*, 1996; Heyward, P. M. *et al.*, 2001). Patch clamp recordings have revealed that mitral cells exhibit intrinsic membrane bistability (Heyward, P. M. *et al.*, 2001; Heinbockel, T. *et al.*, 2004). They spontaneously alternate between a perithreshold upstate membrane potential and a more hyperpolarized (approximately $-10$ mV) downstate membrane potential (Figure 13). Bistability is typically encountered in mitral cells recorded in the depth of the slice (>70 μm from the surface) and may be absent in superficially located cells. Spontaneous or ON-evoked spikes are readily launched from the upstate, and a spike afterhyperpolarization or a hyperpolarization induced by an IPSP or current injection of sufficient amplitude resets the cell to the downstate. In the downstate, more robust ON input is necessary to trigger spikes. The upstate is also characterized by high-frequency (10–50 Hz) subthreshold membrane potential oscillations that appear to be mediated by a balance between opposing $K^+$ currents and TTX-sensitive $Na^+$ currents (Desmaisons, D. *et al.*, 1999; Heyward, P. M. *et al.*, 2001; Balu, R. *et al.*, 2004). Inhibitory synaptic input (e.g., IPSPs) can reset the phase of the oscillations and the timing of mitral cell spikes (Desmaisons, D. *et al.*, 1999). The downstate appears to be maintained by slowly inactivating outward currents (e.g., $K^+$ currents), and the transition from the downstate to the upstate is due to inactivation of the outward currents and activation of regenerative voltage-dependent inward currents (e.g., TTX-sensitive, persistent $Na^+$ currents). The transition from the upstate to the downstate may reflect voltage-dependent inactivation of inward currents and activation of outward currents initiated by action potentials. Other aspects of mitral cell spontaneous activity are discussed below in Oscillations and Synchrony in Main Olfactory Bulb.

Further studies indicated that mitral cell-evoked p0180 activity is regulated by interactions between subthreshold TTX-sensitive $Na^+$ currents and by 4-amonipyridine (4-AP)-sensitive $K^+$ currents, such as transient outward or $I_D$ currents (Balu, R. *et al.*, 2004). In response to sustained depolarization pulses, mitral cells generate intermittent spike clusters at 20–40 Hz, with clusters occurring with variable timing at theta frequencies (1–5 Hz). Brief repolarizations to recover inactivated $Na^+$ currents during sustained depolarizing pulses eliminated spike variability. Brief depolarizing pulses or simulated EPSPs mimicking rhythmic ON input during sniffing elicited highly precise spike clusters. The first EPSP frequently failed to elicit spikes, but decreased the spike threshold for subsequent EPSPs. 4-AP caused spikes to be triggered by the first EPSP but impaired precise spike timing to subsequent EPSPs. 4-AP also abolished intermittent or clustered firing during sustained depolarizations. Taken together, these findings suggest that intrinsic properties of mitral cells yield variable spiking responses to sustained depolarizations but allow temporally precise or phase-locked spiking responses to brief phasic input. Based on this, it has been suggested that mitral cells may be functionally analogous to high-pass filters, preferentially responding to phasic events that occur at theta frequencies (Balu, R. *et al.*, 2004).

Mitral cells also exhibit afterhyperpolarizations p0185 mediated by $Ca^{2+}$-dependent $K^+$ conductances (Maher, B. J. and Westbrook, G. L., 2005). Step depolarization of mitral cells to $+10$ mV elicits outward currents that are attenuated by $Cd^{2+}$ or the SK $K^+$ channel antagonist apamin. This current was reported to be absent in GCs. The SK current could be activated by $Ca^{2+}$ influx via NMDA receptors or voltage-dependent $Ca^{2+}$ channels. Apamin application increased the depolarization-evoked firing frequency of mitral cells. Other studies indicate that mitral cells lack, or have very weak, H-type currents (Djurisic, M. *et al.*, 2004). Mitral cells also express Kv1.3, a rapidly activating, moderately slow

inactivating type of voltage-gated $K^+$ channels (Fadool, D. A. *et al.*, 2004). Mitral cells from Kv1.3-knockout mice have more depolarized resting potentials and smaller, broader spikes in comparison with those from wildtype mice.

s0135 **2.44.4.3 Dendritic Spike Propagation**

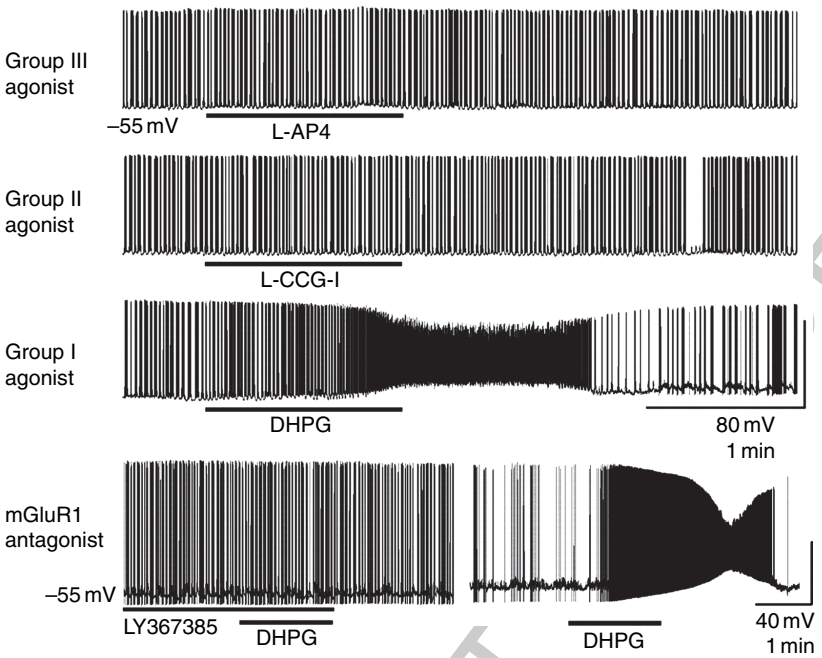
p0190 *In vivo*, odors have been reported to elicit fast prepotentials in mitral cells thought to represent truncated spikes generated in the apical dendrites (see Mori, K., 1987 for review). Similar fast prepotentials have been observed in slices (Chen, W. R. and Shepherd, G. M., 1997). More recent findings in MOB slices demonstrate that both the apical and lateral dendrites of mitral cells actively propagate action potentials. Spike elicited at the soma backpropagate nondecrementally along the apical dendrite and vice versa (Bischofberger, J. and Jonas, P., 1997; Chen, W. R. *et al.*, 1997; Isaacson, J. S. and Strowbridge, B. W., 1998; Debarbieux, F. *et al.*, 2003). The ability of the apical dendrite to generate spikes is due to the presence of TTX-sensitive $Na^+$ channels (Bischofberger, J. and Jonas, P., 1997). These studies suggest that with sufficiently strong ON input, spikes can be initiated in the apical dendrite and conducted to the soma without decrement. However, the site of spike initiation can be controlled by inhibitory inputs to the soma. With leak levels of ON stimulation, spikes are preferentially triggered at the soma, but this can be blocked by IPSPs at the soma or proximal segments of the lateral dendrite (Chen, W. R. *et al.*, 1997; Djurisic, M. *et al.*, 2004). With stronger levels of ON input, inhibitory inputs to the soma shifted the spike initiation site to the apical dendrite. ON-evoked EPSPs by contrast are decremental, and they decrease in amplitude by ~30% over a 300-μm distance in the apical dendrite (Djurisic, M. *et al.*, 2004).

p0195 Similar studies demonstrate actively propagating $Na^+$ spikes in mitral cell lateral dendrites (Margrie, T. W. *et al.*, 2001; Xiong, W. and Chen, W. R., 2002). This suggests that spikes in single mitral cells, via activation of mitral to granule synapses, could conceivably inhibit mitral cells at considerable distances throughout the MOB. However, whether the spike propagation is nondecremental along the full length of the lateral dendrite is unclear as propagation has been reported to be attenuating (Margrie, T. W. *et al.*, 2001; Lowe, G., 2002; Christie, J. M. and Westbrook, G. L., 2003) or nonattenuating (Margrie, T. W. *et al.*, 2001; Xiong, W. and Chen, W. R., 2002; Debarbieux, F. *et al.*, 2003). Spike attenuation was reported to cause activation of A-type $K^+$ channels in the lateral dendrites (Christie, J. M. and Westbrook, G. L., 2003). Regenerative $Ca^{2+}$ currents do not appear to play a role in dendritic spikes (Charpak, S. *et al.*, 2001; Margrie, T. W. *et al.*, 2001; Xiong, W. and Chen, W. R., 2002; Christie, J. M. and Westbrook, G. L., 2003). Local synaptic inhibitory input (GABAergic IPSPs) can block propagation of spikes in the lateral dendrite (Margrie, T. W. *et al.*, 2001; Lowe, G., 2002; Xiong, W. and Chen, W. R., 2002). Such inhibition is more influential when it occurs at the soma and/or proximal dendrites. Thus, inhibitory input to the soma and lateral dendrites may spatially constrain the range and magnitude of lateral inhibition (see also Dendrodendritic Inhibition).

AU26

s0140 **2.44.4.4 Modulation by mGluRs and DA**

p0200 In dissociated cultured rat and frog MOB neuronal preparations, Group I mGluRs increased $Ca^{2+}$ release from internal stores in mitral/tufted cells as well as in MOB interneurons (Geiling, H. and Schild, D., 1996; Carlson, G. C. *et al.*, 1997), or it depolarized and increased the frequency of miniature excitatory postsynaptic currents in mitral cells (Schoppa, N. E. and Westbrook, G. L., 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, P. Q. and Westbrook, G. L., 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 (Figure 12) (Heinbockel, T. *et al.*, 2004). The same study showed that mGluR1 induces a voltage-dependent inward current consisting of multiple components. mGluR1 antagonists also altered mitral cell membrane potential bistability, increasing the duration of the upstates and downstates, and substantially attenuated ON-evoked spikes (Figure 13). These findings suggest that endogenous glutamate tonically modulates MC excitability and responsiveness to ON input via activation of mGluR1. Although DA has no direct effect on resting membrane properties of mitral cells, pharmacological activation of D2 receptors was found to reduce glutamate release from mitral cells onto olfactory bulb interneurons in culture via inhibition of N and/or P/Q HVA $Ca^{2+}$ channels (Davila, N. G. *et al.*, 2003).




f0060 **Figure 12** The group I mGluR agonist (RS)-3,5-dihydroxyphenylglycine (DHPG) depolarizes and increases the firing of mitral cells. Mitral cells were activated by group I, but not group II or III, mGluR agonists. Bath application of the group III mGluR agonist L(+)-2-amino-4-phosphonobutyric acid (AP4; 100 μM) or the group II mGluR agonist (2S,3S,4S)-CCG/(2S,1'S,2'S)-2-(carboxycyclopropyl)glycine (L-CCG-I; 20 μM) did not alter the membrane potential or firing rate of this mouse mitral cells (MC) in current clamp recordings. The same cell was activated by the selective group I agonist DHPG. The selective mGluR1 antagonist ({alpha}S)-{alpha}-amino-{alpha}-[(1S,2S)-2-carboxycyclopropyl]-9H-xanthine-9-propanoic acid (LY367385, 100 μM) blocked the actions of the group I mGluR agonist DHPG (50 μM) in another mouse MC. After washout (>15 min), reapplication of DHPG robustly depolarized and increased MC spontaneous discharge. All experiments were performed in the presence of blockers of fast synaptic transmission: CNQX (10 μM), APV (50 μM), and gabazine (5 μM). Reprinted from Heinbockel, T. *et al.*, 2004, J. Neurophysiol. 92, 3085–3096, with permission from The American Physiological Society.

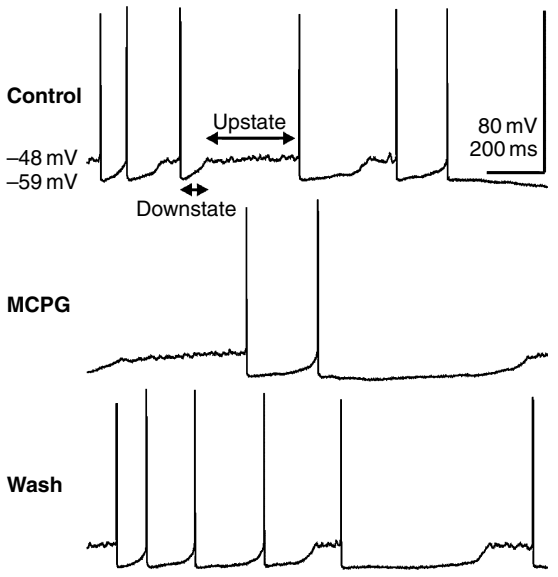


## s0145 2.44.5 Neurophysiology of Neurons in the Granule Cell Layer

### s0150 2.44.5.1 Neuron Types of the GCL

p0205 GCs are axon-less cells with small cell bodies that are mostly tightly packed into row-like aggregates of three to nine somata in the GCL (Reyher, C. K. *et al.*, 1991). More superficially located GCs are also found mixed with mitral cell bodies within the MCL. Most GCs have an apical dendrite that ramifies within the EPL and shorter basal dendrites that ramify within the GCL. A differential sublaminar distribution has been 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, the apical dendrites of deeper GCs terminate preferentially within the deep EPL (Orona, E. *et al.*, 1983; Greer, C. A., 1987). Most GCs contain GABA (Ribak, C. E. *et al.*, 1977), but some contain enkephalin (Bogan, N. *et al.*, 1982; Davis, B. J. *et al.*, 1982). GC apical dendrites receive asymmetrical synapses from, and make symmetrical synapses onto, mitral/tufted cells. GCs also receive asymmetrical synapses from a variety of centrifugal afferents, including inputs from neuromodulatory transmitter systems (see Neurophysiology of Neuromodulatory Inputs to Main Olfactory Bulb) and POC (see Neurophysiology of Primary Olfactory Cortical Inputs to Main Olfactory Bulb) (Price, J. L. and Powell, T. P. S., 1970c). Centrifugal fibers arise from neurons in POC (e.g., PC and anterior olfactory nucleus) and comprise the bulk of synaptic contacts onto GC somata and proximal dendrites within the GCL (Price, J. L. and Powell, T. P. S., 1970c). GCs also receive synapses from the collateral branches of mitral and tufted cell axons, as well as inputs from Golgi, Cajal, and Blanes cells (Price, J. L. and Powell, T. P. S., 1970c). AU27

p0210 The IPL and GCL also contain several interneuron subtypes (short-axon cells; Golgi, Cajal, and Blanes cells) that have dendrites and axons that ramify within the




f0065 **Figure 13** Activation and blockade of mGluRs modulates mitral cell (MC) spontaneous activity and membrane bistability. Upper trace: Current clamp recording showing membrane bistability in a rat MC. Middle trace: Bath application of MCPG (500 μM) reduced the firing frequency of the MC and prolonged the upstates and downstates. Bottom trace: the effects of MCPG were reversible on washout. Reprinted from Heinbockel, T. *et al*., 2004, J. Neurophysiol. 92, 3085–3096, with permission from The American Physiological Society.

EPL, MCL, and GCL (Price, J. L. and Powell, T. P. S., 1970b; Schneider, S. P. and Macrides, F., 1978; Cajal, R. S. Y., 1890; Van Gehuchten, L. E. and Martin, A., 1891; Blanes, T., 1898; López-Mascaraque, L. *et al*., 1990). These cells stain for a number of transmitters, including GABA, VIP, NPY, enkephalin, and somatostatin (see Ennis, M. *et al*., in press for review). With the exception of Blanes cells, very little is known about the functions of the deep interneurons, but all are presumed to be inhibitory. Blanes cells have numerous dendrites emerging from all sides of the soma. The axons from these cells can extend considerable distances, but they typically remain within the GCL (Cajal, R. S. Y., 1911a; 1911b; Pressler, R. T. and Strowbridge, B. W., 2006). The anatomical features of other interneurons in the IPL/GCL are reviewed elsewhere (Ennis, M. *et al*., in press).

s0155 ### 2.44.5.2 Neurophysiology of GCs

p0215 *In vivo* and in slice preparations, GCs spontaneous spiking is relatively infrequent, probably due to their relatively hyperpolarized resting potential (−65 to −75 mV) and appears to be driven primarily by spontaneous glutamatergic input (Wellis, D. P. and Scott, J. W., 1990; Cang, J. and Isaacson, J. S., 2003; Zelles, T. *et al*., 2006; Heinbockel, T. *et al*., submitted). Synaptic input or direct depolarization can elicit $Na^+$ and $Ca^{2+}$ spikes in GCs (Halabisky, B. *et al*., 2000; Pinato, G. and Midtgaard, J., 2003; 2005; Egger, V. *et al*., 2005). By contrast to mitral cells, odor-evoked responses in GCs attenuate rapidly after the first respiratory cycle (Cang, J. and Isaacson, J. S., 2003).

p0220 GCs express $Ca^{2+}$ currents which activate at approximately −60 mV and peak at 0–5 mV (Chen, W. R. *et al*., 2000; Isaacson, J. S. and Vitten, H., 2003). These currents involve both LVA T-type $Ca^{2+}$ currents and HVA $Ca^{2+}$ currents (Isaacson, J. S. and Vitten, H., 2003). T-type currents can be activated by depolarization subthreshold for spike initiation and have been linked to GABA release from GCs (Egger, V. *et al*., 2003). Small subthreshold EPSPs seem to produce $Ca^{2+}$ transients restricted to dendritic spines (Egger, V. *et al*., 2005). These $Ca^{2+}$ transients appear to involve several sources, including LVA and HVA $Ca^{2+}$ channels, NMDA receptors, and $Ca^{2+}$-induced $Ca^{2+}$ release (Egger, V. *et al*, 2005). Sufficiently large EPSPs can trigger an all-or-none LTS that propagates throughout the GC dendrites (Egger, V. *et al*., 2005). LTSs in GC soma have been described in amphibians (Pinato, G. and Midtgaard, J., 2003; 2005).

p0225 GC activity is strongly regulated by several $K^+$ conductances. They have a strong transient A-type $K^+$ current, $I_A$ (Schoppa, N. E. and Westbrook, G. L., 1999). $I_A$ in these cells activates at approximately −44 mV, at of near the threshold for spike generation AU28 (−47 mV). Many $I_A$ channels are only half-inactivated at GC resting membrane potential, and thus are available to affect depolarizing inputs (Schoppa, N. E. and Westbrook, G. L., 1999). Blockade of $I_A$ with 4-AP decreases the lag or delay for evoked spikes. The $I_A$ channels are expressed in the distal dendrites of GCs where they tend to counter brief depolarizing synaptic inputs (see below). AU29 BK-type or high-conductance $Ca^{2+}$-activated $K^+$ currents involved in spike repolarization of afterhyperpolarization are engaged in GCs by strong depolarization or activation of NMDA receptors (Isaacson, J. S. and Murphy, G. J. 2001). Anatomically, gap junctions have been reported among GCs (Reyher, C. K. *et al*., 1991), although electrophysiological studies found no evidence for electrotonic coupling (Schoppa, N. E., 2006). GCs in the GCL are potently activated by mGluR1 agonists, which depolarize and increase the firing rate of

these cells (Heinbockel, T. *et al.*, submitted). By contrast, mGluR1 antagonists reduce mitral/tufted cell-evoked excitation of GCs.

s0160 #### 2.44.5.3 Neurophysiology of Blanes Cells

p0230 Blanes cells are neurophysiologically distinct from GCs (Pressler, R. T. and Strowbridge, B. W., 2006). They have lower input resistance, more depolarized resting potential, and more hyperpolarized spike threshold than GCs. Stimulation of Blanes cells elicits monosynaptic GABAergic IPSPs in GCs, but Blanes cells do not receive reciprocal input from GCs. These cells generate prominent afterdepolarizations (ADPs) after action potentials that are triggered by $Ca^{2+}$ influx through non-L-type channels. ADPs were suppressed by flufenamic acid, a blocker of nonspecific cation currents ($I_{CAN}$). Taken together, these findings suggest that the ADP is mediated by a $Ca^{2+}$-dependent $I_{CAN}$. Brief depolarization triggers unusually prolonged (up to 44 min) persistent spiking in Blanes cells. Persistent firing could also be triggered by excitatory synaptic input elicited by stimulation in the GCL or the GL. Stimuli that evoked persistent firing in Blanes cells also produced prolonged barrages of IPSCs in GCs. These findings indicate that Blanes cells play a major role in prolonged modulation of the excitability state of GCs, which in turn would impact on the activity of mitral/tufted output neurons. Because Blanes cell inputs to GCs appear to be concentrated in the GCL (i.e., near the somata/proximal dendrites), they may be targeted by these inputs and/or play a major role in modulating centrifugal feedback input to GCs from POC. Thus, the activity state of Blanes cells may provide a gate on excitatory feedback projections from POC to GCs, which in turn, would modulate GC inhibition of mitral/tufted cells.

s0165 ### 2.44.6 Dendrodendritic Transmission Between Mitral/Tufted Cells and Granule Cells

s0170 #### 2.44.6.1 Overview of Mitral/Tufted Cell–GC Dendrodendritic Interactions

p0235 The majority of 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, J. L. and Powell, T. P. S., 1970b; 1970c; 1970d). These synapses are mostly reciprocal (Hirata, Y., 1964; Rall, W. *et al.*, 1966; Price, J. L. and Powell, T. P. S., 1970d; Woolf, T. B. *et al.*, 1991) and therefore occur in roughly equal proportion (Jackowski, A. *et al.*, 1978). One mitral/tufted cell can therefore receive feedback inhibition as well as lateral inhibition from GCs that are excited by other mitral/tufted cells.

#### 2.44.6.2 Excitatory Transmission from Mitral/Tufted Cells to GCs s0175

Spike-evoked $Ca^{2+}$ transients in mitral cells, and presumably glutamate release, is abolished by $Cd^{2+}$ but not $Ni^{2+}$, indicating that it requires activation of HVA $Ca^{2+}$ channels (Isaacson, J. S. and Strowbridge, B. W., 1998). Intracellular $Ca^{2+}$ buffering in mitral cells indicates that the $Ca^{2+}$ channels that trigger dendritic glutamate release are located nearby active release sites (Isaacson, J. S. and Strowbridge, B. W., 1998). In normal or $Mg^{2+}$-free extracellular media, stimulation of mitral/tufted cells evokes dual-component EPSCs in GCs, consisting of a fast AMPA receptor component and a slow NMDA receptor component (Isaacson, J. S. and Strowbridge, B. W., 1998; Schoppa, N. E. *et al.*, 1998; Aroniadou-Anderjaska, V. *et al.*, 1999a; Chen, W. R. *et al.*, 2000; Isaacson, J. S., 2001). AMPA receptors in cultured GCs desensitize rapidly and have little or no $Ca^{2+}$ permeability (Blakemore, L. J. and Trombley, P. Q., 2003), suggesting that GC AMPA receptors must include GluR2 subunits, which regulate $Ca^{2+}$ permeability (Jardemark, K. *et al.*, 1997). The AMPA receptor synaptic component evoked by mitral/tufted cell input is less effective than the NMDA receptor component in evoking spikes in GCs, especially in $Mg^{2+}$-free conditions (Schoppa, N. E. *et al.*, 1998). As noted above, block of $I_A$ enhances the ability of the AMPA receptor component to trigger spikes in GCs (Schoppa, N. E. and Westbrook, G. L., 1999). Paired-pulse stimulation of mitral cells can produce either facilitation or depression of the GC excitatory response to the second pulse, but on average leads to paired-pulse facilitation (Dietz, S. B. and Murthy, V. N., 2005). With repetitive stimulation trains, mitral to GC responses were suppressed less than GC to mitral cell inhibitory responses. Mitral/tufted cell to GC transmission may be modulated by mGluRs and monoaminergic transmitters (see Section Neurophysiology of Neuromodulatory Inputs to Main Olfactory Bulb). Activation of p0240

Group III mGluR was reported presynaptically to decrease mitral cell to GC synaptic transmission (Trombley, P. Q. and Westbrook, G. L., 1992).

s0180 **2.44.6.3 Inhibitory Transmission from GCs to Mitral/Tufted Cells**

p0245 Activation of GCs evokes IPSPs/IPSCs in mitral cells mediated by activation of $GABA_A$ receptors (Chen, W. R. *et al.*, 2000; Isaacson, J. S. and Vitten, H., 2003; Dietz, S. B. and Murthy, V. N., 2005). Paired-pulse or repetitive activation of GCs typically produces paired-pulse inhibition of mitral cell synaptic responses; i.e., the response to the second or subsequent pulses are smaller than that to the first (Isaacson, J. S. and Vitten, H., 2003; Dietz, S. B. and Murthy, V. N., 2005). Pharmacological activation of $GABA_B$ receptors on GCs has been reported to reduce GABA release from these cells via inhibition of HVA $Ca^{2+}$ currents (Isaacson, J. S. and Vitten, H., 2003).

s0185 **2.44.6.4 Dendrodendritic Inhibition**

s0190 ***2.44.6.4.1 Self-inhibition***

p0250 Intracellular stimulation of single mitral cells in the presence or absence of TTX results in a dendrodendritically mediated feedback IPSPs/IPSCs, i.e., self-inhibition or feedback inhibition (Isaacson, J. S. and Strowbridge, B. W., 1998; Schoppa, N. E. *et al.*, 1998; Chen, W. R. *et al.*, 2000; Halabisky, B. *et al.*, 2000; Dietz, S. B. and Murthy, V. N., 2005). Subsequent studies demonstrated that TTX has opposite effects on self-inhibition that depend upon the strength of the mitral cell depolarizing pulse; i.e., the amount of glutamate released by the mitral cell (Halabisky, B. *et al.*, 2000). Short-pulse (2–3 ms) self-inhibition is reduced, whereas long-pulse (>25 ms) inhibition is enhanced, by TTX. The feedback inhibition is of long duration (1–2 s) and consists of a flurry of individual IPSPs/IPSCs. The slow kinetics suggest that the feedback IPSPs/IPSCs is mediated by asynchronous GABA release from multiple GCs (Schoppa, N. E. *et al.*, 1998). In normal extracellular levels of $Mg^{2+}$, the self-inhibition is reduced to similar levels by AMPA or NMDA receptor antagonism and is abolished when antagonists to both receptors are applied (Isaacson, J. S. and Strowbridge, B. W., 1998). $Mg^{2+}$-free conditions enhance self-inhibition and cause it to be dominated by activation of NMDA receptors; under these conditions, AMPA receptors have only a minor effect of the magnitude of self-inhibition (Isaacson, J. S. and Strowbridge, B. W., 1998; Schoppa, N. E. *et al.*, 1998; Chen, W. R. *et al.*, 2000; Isaacson, J. S., 2001;; Halabisky, B. and Strowbridge, B. W., 2003). Similar findings were obtained for tufted cell self-inhibition (Christie, J. M. *et al.*, 2001). As will be discussed below, lateral inhibition has been reported to be strongly regulated by the A current in GCs. Self-inhibition has been reported to be unaffected (Halabisky, B. *et al.*, 2000) or enhanced (Schoppa, N. E. and Westbrook, G. L., 1999; Isaacson, J. S., 2001) by blockers of $I_A$. As discussed below, self-inhibition is strongly regulated by $I_A$ in GCs. Self-inhibition is unaffected by the L-type $Ca^{2+}$ channel antagonist (nifedipine) or T- or R-type $Ca^{2+}$ channel antagonists (50 μM $Cd^{2+}$) but is markedly attenuated by the P/Q- and N-type antagonist ω-conotoxin MVIIC (Isaacson, J. S. and Strowbridge, B. W., 1998). Self-inhibition is reduced by $GABA_B$ receptor agonists, presumably by reducing HVA currents in GCs (Isaacson, J. S. and Vitten, H., 2003). It is also reduced by mGluR antagonists (Heinbockel, T. *et al.*, submitted). AU30

***2.44.6.4.2 Lateral inhibition*** s0195

p0255 Stimulation of one mitral cell in the presence of TTX results in a dendrodendritically mediated mitral-granule-mitral cell IPSPs/IPSCs, i.e., feedforward or lateral inhibition (Isaacson, J. S. and Strowbridge, B. W., 1998; Urban, N. N. and Sakmann, B., 2002). Like self-inhibition, lateral inhibition in $Mg^{2+}$-free conditions is completely abolished by NMDA receptor antagonists; in normal extracellular media, AMPA receptors seem to play a more important role when the lateral inhibition is evoked by weaker stimulation (Isaacson, J. S. and Strowbridge, B. W., 1998; Schoppa, N. E. *et al.*, 1998). The spatial extent of lateral inhibition among mitral cells has been reported to be greater than that for tufted cells. Tufted cell lateral inhibition is limited to several glomerular widths (<400 μm) as opposed to 750 μm for mitral cells (Christie, J. M. *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, K. *et al.*, 1983; Orona, E. *et al.*, 1984). The $I_A$ current strongly regulates the duration of lateral inhibition and the role of AMPA receptors. 4-AP reduces the duration of lateral inhibition and increases the contribution of AMPA receptors. As noted above, 4-AP blocks $I_A$, which normally occludes or counters the brief AMPA receptor-mediated depolarization and spiking in GCs. $I_A$ blockade disinhibits the AMPA receptor-mediated synaptic component, reduces the latency

of evoked spikes, and therefore leads to more rapid and synchronous GABA release from GCs (Schoppa, N. E. and Westbrook, G. L., 1999). Consequently, the 4-AP reduces the contribution of the slow kinetics of the NMDA receptor-mediated synaptic component to GC GABA release. The results were somewhat different for self-inhibition, in which the amplitude of early IPSC component was markedly increased, as was the total duration of the IPSC. Blockade of SK currents in mitral cells enhances lateral inhibition (Maher, B. J. and Westbrook, G. L., 2005).

s0200 #### 2.44.6.4.3 Role of $Ca^{2+}$ influx through NMDA receptors and voltage-dependent $Ca^{2+}$ channels

p0260 Later studies demonstrated that $Ca^{2+}$ influx through the NMDA receptor can directly trigger GABA release from GCs (Halabisky, B. *et al.*, 2000; Chen, W. R. *et al.*, 2000; Isaacson, J. S., 2001). Thus, NMDA applied focally into the EPL in the presence of the HVA $Ca^{2+}$ channel blocker, $Cd^{2+}$, elicited IPSCs in mitral cells. Similar results were obtained in $Mg^{2+}$-free conditions when flash photolysis was used to increase intracellular $Ca^{2+}$ in the mitral cell (Chen, W. R. *et al.*, 2000; Isaacson, J. S., 2001); the photolysis-induced IPSC could be blocked by NMDA receptor antagonists or $Cd^{2+}$ (Chen, W. R. *et al.*, 2000; Isaacson, J. S., 2001). The NMDA-evoked IPSC did not depend on $Ca^{2+}$ release from internal stores as it was unaffected by thapsigargin (Halabisky, B. *et al.*, 2000; Chen, W. R. *et al.*, 2000). However, IPSCs elicited by NMDA or KCl application in the GCL were blocked by $Cd^{2+}$ (Halabisky, B. *et al.*, 2000). These findings suggest that $Ca^{2+}$ influx via NMDA receptors near dendrodendritic synapses, presumably on GC spines, is directly coupled to GABA release. However, depolarization at more remote sites (GC somata/proximal dendrites) induces $Ca^{2+}$ influx via HVA $Ca^{2+}$ channels.

s0205 #### 2.44.6.4.4 Local vs. global modes of dendrodendritic inhibition

p0265 Current views are that weak stimulation producing small synaptic responses in GCs, and thus $Ca^{2+}$ influx into isolated GCs spines, triggers GABA release and inhibition of mitral cell dendrites that are synaptically coupled to those spines. Such inhibition would tend to be spatially localized. Both NMDA receptors and voltage-dependent $Ca^{2+}$ channels can provide the $Ca^{2+}$ influx necessary for GABA release from spines. By contrast, stronger levels of mitral/tufted cell input that generate actively propagating $Na^{+}$ spikes would produce more global or widespread inhibition mitral/tufted cells (Chen, W. R. *et al.*, 2000; Egger, V. *et al.*, 2003). As noted above, sufficiently large EPSPs subthreshold for $Na^{+}$ spikes can trigger an all-or-none LTS that propagates throughout the GC dendrites (Egger, V. *et al.*, 2005). Thus, the LTS is an additional candidate for global lateral inhibition. AU31

#### 2.44.6.4.5 Temporal modulation of dendrodendritic inhibition s0210

p0270 In slices, paired-pulse mitral cell stimulation experiments show that self-inhibition elicited by the second pulse was markedly reduced and recovered with a time constant of ~6 s (Dietz, S. B. and Murthy, V. N., 2005). This finding may, in part, account for the decrement in GABAergic synaptic input to mitral cells across respiratory cycles during odor stimulation (Cang, J. and Isaacson, J. S., 2003). The observation that GC odor responses subside across sniffs may also lead to reduced dendrodendritic inhibition during respiration. Thus, the strength of dendrodendritic inhibition is likely to be temporally modulated across with respect to respiration. Other studies indicate that higher frequency local $\gamma$-oscillatory activity generated by mitral cell–GC interactions may also modulate GABAergic inhibition. Local $\gamma$-frequency stimulation in the GCL or ELP can facilitate mitral cell feedback and lateral inhibition by relieving the $Mg^{2+}$ block of NMDA receptors on GCs (Halabisky, B. and Strowbridge, B. W., 2003).

## 2.44.7 Neurophysiology of New, Adult-Born Neurons s0215

p0275 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, J. W., 1968; Altman, J., 1969; Bayer, S. A., 1983). In adults, interneurons (primarily GCs and PG cells) are continually generated from these progenitor cells, and their offspring generated en route migrates to the MOB within the rostral migratory stream (RMS; Luskin, M. B., 1993; Lois, C. and Alvarez-Buylla, A., 1994; Smith, T. and Lushkin, M. B., 1998; Wichterle, H. *et al.*, 2001). 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, H. *et al*., 2001). 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, O. *et al*., 2003; Carleton, A. *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 and a reduced MOB size, have been shown to exhibit impaired odor discrimination (Gheusi, G. *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, C. *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.

s0220

## 2.44.8 Neurophysiology of Primary Olfactory Cortical Inputs to Main Olfactory Bulb

p0280 Extrinsic afferent input to MOB, also referred to as centrifugal fibers, can be subdivided into two classes: (1) inputs arising from nonolfactory, so-called neuromodulatory transmitter systems including ACh, norepinephrine (NE), and 5-HT (these neuromodulatory inputs are discussed below in Neurophysiology of Neuromodulatory Inputs to Main Olfactory Bulb), and (2) feedback inputs arising from olfactory-related structures, in particular those arising from POC. Feedback projections to MOB from POC arises predominantly from glutamatergic, pyramidal neurons in layers II and III of piriform cortex, as well as other POC structures (for review, see Ennis, M. *et al*., in press). These projections massively target GCs, where they form asymmetrical synapses on the cell bodies, basal dendrites, and spines of GCs (Price, J. L. and Powell, T. P. S., 1970a). Activation of these feedback projections produces a negative field potential recorded in the GCL (Walsh, R. R., 1959; Nakashima, M. *et al*., 1978), as expected if excitatory currents are flowing into GCs. Similar stimulation elicits IPSPs in mitral cells (Yamamoto, C. *et al*., 1963; Nicoll, R. A., 1971; Mori, K. and Takagi, S. F., 1978), due to excitation of GCs, followed by GABA release onto mitral cells, i.e., dendrodendritic inhibition (Halász, N. and Shepherd, G. M., 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, N. and Ennis, M., 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, D. I. B. and Hagbarth, K. E., 1955; von Baumgarten, R. *et al*, 1962).

s0225

## 2.44.9 Oscillations and Synchrony in Main Olfactory Bulb

s0230

### 2.44.9.1 Oscillations

p0285 Oscillations and synchronous activity are characteristic features of spontaneous and odor-driven activity in the MOB and other olfactory structures. A detailed consideration of oscillations in the MOB is beyond the scope of the present review and has recently been reviewed elsewhere (Lledo, P. M. *et al*., 2005; Gelperin, A., 2006; Kepecs, A. *et al*., 2006). Prominent oscillatory activity is present in MOB field potentials, which primarily reflect synchronized subthreshold membrane potentials arising from large neuronal populations, or in membrane potential or spike activity of individual MOB neurons. Sensory input to the olfactory system occurs as a result of respiration which by its very nature is cyclical or rhythmical. Relatively low-frequency oscillations synchronized to respiration, in the presence and absence of odors, occur in the theta band (2–12 Hz). Higher frequency oscillations, superimposed on the theta, occur in the beta (15–40 Hz) and gamma (30–80 Hz) bands. Beta frequency oscillations are relatively poorly understood, but have recently been discussed elsewhere (Neville, K. R. and Haberly, L. B., 2003; Martin, C. *et al*., 2004; Fletcher, M. L. *et al*., 2005). Lower frequency oscillatory (0.1–0.03 Hz) and synchronous activity has been observed in MOB slices under certain conditions (Puopolo, M. and Belluzzi, O., 2001).

s0235 ***2.44.9.1.1 Theta rhythm***

p0290 In the MOB, 2 to 12 Hz oscillations are referred to as theta principally because they occupy a highly overlapping frequency band with hippocampal theta oscillations (Kay, L. M. and Laurent, G., 1999; Kay, L. M., 2003; 2005). As noted above, theta frequency oscillations are driven by, and thus synchronized or phase-locked with, respiration. Therefore, the specific theta frequency varies with the sniffing frequency (i.e., the pattern of airflow across the nasal epithelium) and includes components related to low-frequency (1–3 Hz) passive sniffing as well as a higher frequency component (5–12 Hz) characteristic of active investigative sniffing (Adrian, E. D., 1950; Welker, W. I., 1964; Macrides, F. *et al.*, 1982; Eeckman, F. H. and Freeman, W. J., 1990; Kay, L. M. and Laurent, G., 1999; Kay, L. M., 2003). As noted earlier, mitral cell subthreshold membrane potential oscillations and/or spike activity is synchronized with certain phases of the respiratory cycle. Manipulations that impair or disrupt respiratory-driven input to the MOB disrupts mitral cell activity and decouples it from the respiratory cycle (Philpot, B. D. *et al.*, 1997). Thus, theta oscillations appear to be driven by the pattern of respiratory-driven input to MOB. However, intrinsic membrane and synaptic properties enhance the ability of some MOB neurons to entrain or synchronize with rhythmical respiratory-driven activity. For example, ET cells in MOB slices intrinsically generate spike bursts at frequencies ranging from ~1 to 8 Hz, and readily entrain to patterned sensory input over this same range. Thus, the properties of these cells may allow them to discharge in synchrony with the respiratory cycle.

s0240 ***2.44.9.1.2 Gamma rhythm***

p0295 Gamma oscillations arise during odorant or direct ON stimulation and appear to be generated intrinsically in the MOB. Thus, they persist when centrifugal input to the bulb is severed or impaired (Gray, C. M. and Skinner, J. E., 1988; Neville, K. R. and Haberly, L. B., 2003). As with theta oscillations, odor- or ON-evoked gamma oscillations are apparent in the EEG, MOB field potentials, and subthreshold membrane potential and spiking activity of mitral cells (Adrian, E. D., 1950; Eeckman, F. H. and Freeman, W. J., 1990; Kay, L. M. and Freeman, W. J., 1998; Kashiwadani, H. *et al.*, 1999; Debarbieux, F. *et al.*, 2003; Friedman, D. and Strowbridge, B. W., 2003; Neville, K. R. and Haberly, L. B., 2003; Lagier, S. *et al.*, 2004; Martin, C. *et al.*, 2004; Fletcher, M. L. *et al.*, 2005). Current source-density analyses indicate that the gamma oscillations in MOB field potentials primarily reflect synaptic currents flowing in GCs (Neville, K. R. and Haberly, L. B., 2003). Multisite recordings demonstrated that the phase of gamma oscillation may vary in different parts of the MOB, especially at low odor concentrations. Gamma oscillations are thought to arise primarily as a result of rhythmic or reverbatory interactions between mitral/tufted cells and inhibitory interneurons, chiefly GCs (Friedman, D. and Strowbridge, B. W., 2003; Neville, K. R. and Haberly, L. B., 2003; Lagier, S. *et al.*, 2004). Mitral cell activity is synchronized with $\gamma$-frequency MOB field potentials and also with GABAergic synaptic input (Lagier, S. *et al.*, 2004). The duration of mitral cell to GC synaptic input occurs over a time course of approximately one-half cycle of the gamma oscillation. Gamma oscillatory activity in mitral cells is suppressed or attenuated by glutamate receptor antagonists (decreasing mitral/tufted cell excitation of GCs) or by $GABA_A$ receptor antagonists (blocking GC-mediated inhibition of mitral/tufted cells) (Friedman, D. and Strowbridge, B. W., 2003; Lagier, S. *et al.*, 2004). 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 $\gamma$-frequency oscillations were increased; and discrimination of closely related mixtures of alcohols after training was poor relative to normal mice (Nusser, Z. *et al.*, 2001). Gamma oscillations also appear to involve electrical synapses as they are suppressed by gap junction inhibitors (Friedman, D. and Strowbridge, B. W., 2003). Consistent with this, gamma oscillations are disrupted in connexin36-knockout mice (Hormuzdi, S. G. *et al.*, 2001). Intrinsic membrane properties of mitral cells may facilitate gamma oscillatory activity and spiking. When near spike threshold, mitral cells exhibit intrinsically generated subthreshold membrane potential oscillations in the $\gamma$-frequency range (Chen, W. R. and Shepherd, G. M., 1997; Desmaisons, D. *et al.*, 1999).

## 2.44.9.2 Synchrony

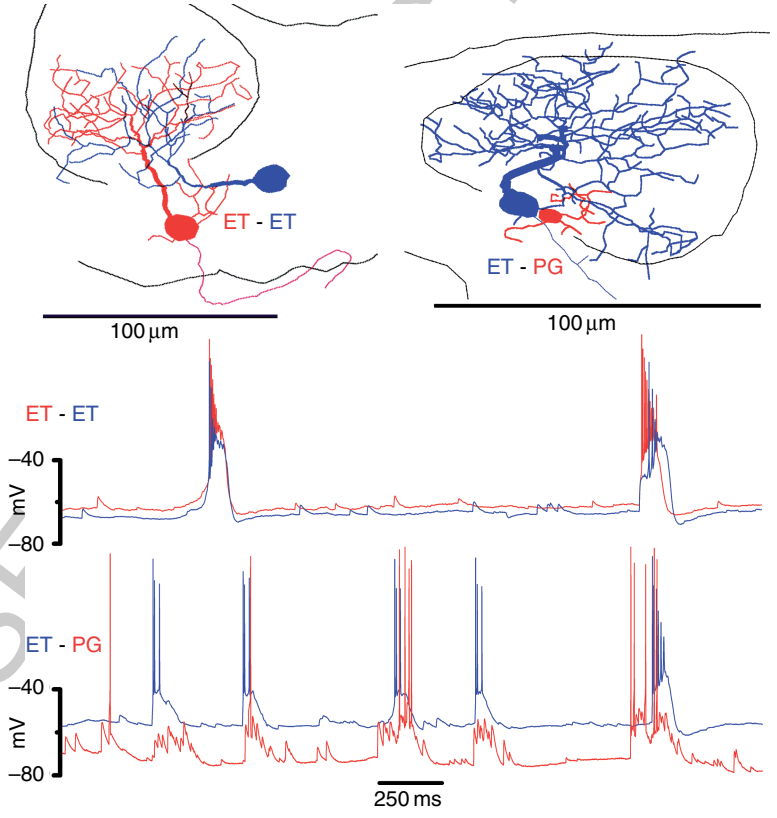
s0245

p0300 Synchrony can be defined as a temporal coincidence between two or more events that have a low probability of occurring by random or chance. Neurons involved in the detection and processing of odors show temporally correlated or synchronized activity,

a feature that is expected to have functional relevance for understanding the population code in the olfactory system (Laurent, G., 2002).

s0250 ***2.44.9.2.1 Synchrony among JG cells***

p0305 JG neurons associated with the same glomerulus exhibit highly synchronous spontaneous activity. Simultaneous recordings of ET–PG or ET–SA cell pairs demonstrated that spikes in ET cells drive synchronous activity in PG and SA cells, but only if the dendrites of both cells ramified in the same glomerulus (Figure 14) (Hayar, A. *et al.*, 2004b). This intraglomerular synchronous activity is driven by glutamatergic input from ET cells to PG/SA cells and is abolished by AMPA receptor antagonists. Similar studies revealed that spontaneous spikes and subthreshold membrane potential activity (i.e., EPSPs, IPSPs) among ET cells of the same glomerulus is highly synchronous (Figure 14) (Hayar, A. *et al.*, 2004b; 2005). Interestingly, the frequency of spontaneous inhibitory input to ET cells, which primarily originates from PG cells, occurs around 50 Hz ($\gamma$ frequency) and is similar to the frequency of ON-evoked $\gamma$-oscillations in mitral cells (mean 45 Hz, Lagier, S. *et al.*, 2004). Although spontaneous synaptic input can synchronize ET cells, synchrony among these cells persists when ionotropic glutamate and GABA receptors are blocked (Hayar, A. *et al.*, 2004b; 2005). Additional electrophysiological results demonstrated that ET cells of the same glomerulus are electrotonically coupled via gap junctions with a relatively small conductance (0.1 nS). Spontaneous synchrony among ET cells is abolished by the gap junction blocker carbenoxolone (Hayar, A. *et al.*, 2005). These results are consistent with anatomical evidence for gap junctions between mitral/tufted cell apical dendrites (see below). Unlike mitral cells, which AU35 exhibit a narrow window of spike-to-spike correlation (see below; Schoppa, N. E. and Westbrook, G. L., 2002), ET cells exhibit a broader window of




f0070 **Figure 14** Synchronous activity among juxtaglomerular (JG) cells associated with the same glomerulus. Upper panel shows reconstructions of the recorded cells (left, two external tufted (ET) cells; right, an ET cell and a periglomerular (PG) cell). Middle panel: Dual whole-cell current clamp recording from two ET cells (red and blue traces, respectively) showing correlation of spike bursts and membrane potentials. Lower panel: Dual whole-cell current clamp recordings show that EPSP bursts and spikes in a PG cell (red trace) are synchronous with spike bursts in an ET cell (blue trace).

burst-to-burst correlation. The narrow window of correlation among mitral cells is due to the fact that mitral cell spikes induced fast EPSPs in other mitral cells (Schoppa, N. E. and Westbrook, G. L., 2002). In contrast, ET cells seem to communicate mainly via slow inward currents produced by gap junctions with relatively low conductance. Therefore, one potential function of gap junctions in ET cells is to filter fast spiking activity and propagate slow membrane potential oscillations, which are driven mainly by persistent $Na^+$ current (Hayar, A. *et al.*, 2004a).

s0255 ***2.44.9.2.2 Synchrony among mitral cells***

p0310 Synchronous activity in the mammalian MOB occurs among mitral cells that send an apical dendrite to receive input from a single glomerulus. By using simultaneous recordings from pairs of mitral cells, it has been shown that pairs with apical dendrites in the same glomerulus display highly synchronized synaptic and/or spike activity, whereas pairs associated with different glomeruli do not. As reviewed earlier, mitral cells associated with the same glomerulus exhibit synchronous AMPA receptor-mediated LLDs that spontaneously occur at a frequency of ~1 Hz (Carlson, G. C. *et al.*, 2000). LLDs (Figure 6) are generated by network activity in the glomeruli and could be elicited by ON or antidromic stimulation, but never by depolarization of single mitral cells. Subsequent studies demonstrated that slow (2 Hz) oscillations and spikes elicited by single ON shocks or NMDA application were synchronous among mitral cells of the same glomerulus; cells associated with distant glomeruli did not exhibit synchrony, while those associated with adjacent glomeruli exhibited temporally correlated by not AU36 synchronous oscillations (Schoppa, N. E. and Westbrook, G. L., 2001; 2002). The synchronous activity among mitral cells was abolished by AMPA receptor antagonists and dampened by mGluR antagonists (Schoppa, N. E. and Westbrook, G. L., 2001; 2002). These and later studies indicated that mitral cell apical dendrites in the same glomerulus exhibit electrotonic coupling (Schoppa, N. E. and Westbrook, G. L., 2002; Christie, J. M. *et al.*, 2005). In mouse MOB slices, current injections into one cell elicited correlated spikes in a second mitral cell if the dendrites extended into the same glomerulus. Such synchrony, however, was absent in slices from connexin36-knockout mice (Christie, J. M. *et al.*, 2005). Connexins are a member of gap junction proteins involved in electrical signaling between cells. The preceding finding is consistent with the presence of high levels of connexin36 in MOB neurons, and specifically in mitral/tufted dendrites (Condorelli, D. F. *et al.*, 1998; 2000; Belluardo, N. *et al.*, 2000; Rash, J. E. *et al.*, 2000; Teubner, B. *et al.*, 2000; Zhang, C. and Restrepo, D., 2003; Christie, J. M. *et al.*, 2005). Other studies have also reported gap junctions in, or between, mitral/tufted cell dendrites (Paternostro, M. A. *et al.*, 1995; Miragall, F. *et al.*, 1996; Kosaka, T. and Kosaka, K., 2003; 2004). In slices from wildtype, AU37 but not connexin36-knockout mice, a spike elicited in one mitral cell evoked an AMPA receptor-mediated potential ($D_{AMPA}$) in the second mitral cell (Christie, J. M. *et al.*, 2005). Correlated spiking in connexin36-knockout mice could be reinstated by boosting glutamate levels with uptake inhibitors. Taken together, these findings indicate that electrical coupling is necessary to drive $D_{AMPA}$, which in turn, drives correlated spiking among mitral cells. Thus, the apical dendrites of mitral cells generate a unique form of electrochemical transmission. The dependence of correlated spiking on AMPA receptors is a distinct feature of mitral–mitral cell synchrony.

p0315 GABAergic inhibition is also thought to play an important role in synchronizing mitral cell activity. As noted earlier, $\gamma$-frequency oscillation and spiking is a prominent feature of mitral cell odor-evoked activity. Spontaneous synchronous IPSPs can reset the phase of subthreshold membrane oscillations and synchronize the firing of multiple mitral cells (Desmaisons, D. *et al.*, 1999). Correlated IPSPs might also contribute to the odor-elicited high-frequency oscillations in the olfactory bulb of adult rats (Fletcher, M. L. *et al.*, 2005). The frequency of ON-evoked local field potential oscillations (mean 45 Hz, Lagier, S. *et al.*, 2004) recorded in the MCL is attributed to rhythmic dendrodendritic granule to mitral cell inhibition. Unlike glomerular mechanisms, GABAergic inhibition appears to synchronize mitral cells associated with different glomeruli. Mitral cell associated with different glomeruli can be synchronized by rhythmic stimulation of the ON at theta frequencies (Schoppa, N. E., 2006). Such synchrony does not depend upon electrotonic coupling, but appears to be driven by synchronous IPSPs from GCs, such that synchronous spikes in mitral cells occur during the recovery from the synchronous IPSP. One possible function of spike synchrony among mitral cells of different odorant receptor specificities is to provide a mechanism for downstream cortical neurons to decode information about different odorant receptors (Schoppa, N. E., 2006). As would be required by such a mechanism, labeling

studies suggest that each pyramidal cell in the anterior piriform cortex receives anatomical connections from mitral cells with different odorant receptor specificities (Zou, Z. *et al.*, 2001). Assuming that pyramidal cells in the olfactory cortex have synaptic integration windows comparable to other pyramidal neurons (e.g., ~7 ms), synchrony among mitral cells would promote the summation of EPSPs and the likelihood that cortical neurons fire action potentials in response to input from activated mitral cells of different odorant receptor specificities.

s0260 #### 2.44.9.3 Oscillations, Synchrony and Odor Coding

p0320 Temporal firing patterns, including rhythmic oscillations and neuronal synchronization, are thought to be important in sensory information processing (Alonso, J. M. *et al.*, 1996; Konig, P. *et al.*, 1996; Roy, S. A. and Alloway, K. D., 2001) including odor coding (for review, see Friedrich, R. W., 2002). Rhythmic activity and synchrony are thought to coordinate intra- and interstructural communication. Olfactory information is thought to be encoded, at least in part, by network oscillations (Wehr, M. and Laurent, G., 1996; Kauer, J. S., 1998; Kay, L. M. and Laurent, G., 1999). In the first stage of olfactory processing, network interactions within each glomerulus act to synchronize the discharge of mitral cells associated with that glomerulus to the theta pattern of rhythmical sensory input. By temporally binding the discharge of mitral cells, such synchrony would maximize the transfer of sensory input onto the output neurons. This, in turn, would facilitate faithful transfer of glomerular sensory input to higher order olfactory structures (i.e., POC). In other words, temporal summation of EPSPs produced by synchronous spikes from the glomerular ensemble of mitral/tufted cells would increase the likelihood of spike initiation in postsynaptic POC neurons. Glomerular synchrony may be a particularly important amplification mechanism when odor concentrations are insufficient to activate all mitral cells of a particular glomerulus. Odors typically activate multiple glomeruli, but the mechanism that drives the sensory input (respiration) is common to all glomeruli. Does this imply that oscillations and synchrony should be phase-locked across responsive glomeruli? This does not seem to be the case as the widespread distribution of ORNs and their odorant response kinetics produce temporal variations in odor response properties in different glomeruli. Thus, different glomeruli activated by the same odorant exhibit temporally distinct response profiles (Spors, H. *et al.*, 2006). It is likely, therefore, that at least initially there will be temporal differences in the phase of oscillatory neuronal activity and synchrony among neurons in different responsive glomeruli. In addition, both glomerular odor activity patterns and discharge of mitral cells change within and across sniffs (Friedrich, R. W., 2002; Spors, H. *et al.*, 2006), and as noted above, the phase of gamma oscillations may not always be uniform throughout the MOB. Neurons in POC appear to receive convergent input from multiple glomeruli (Zou, Z. *et al.*, 2001; Illig, K. R. and Haberly, L. B., 2003). Temporal variations in activity patterns from different glomeruli, via mitral/tufted cells, may be an important element in odor recognition and discrimination.

## 2.44.10 Neurophysiology of Neuromodulatory Inputs to Main Olfactory Bulb s0265

p0325 MOB receives extrinsic inputs from cholinergic, noradrenergic, and serotonergic groups in the basal forebrain and brainstem. As these inputs innervate neurons in multiple layers of MOB, and therefore modulate multiple neuronal subtypes, their physiological effects are collectively reviewed here.

### 2.44.10.1 Cholinergic Inputs to MOB s0270

p0330 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, K. A., 1984; Shipley, M. T., and Adamek, G. D., 1984). At least two distinct transmitter-specific populations of NDB neurons project to the MOB (Zaborszky, L., *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, L., *et al.*, 1986). Choline acetyltransferase, the biosynthetic enzyme for ACh synthesis, is located in axons distributed across most layers of the MOB, except the ONL; cholinergic fibers are especially heavy in the GL and IPL (Ennis, M. *et al.*, in press). As reviewed elsewhere, muscarinic and nicotinic receptors are found in most layers of MOB (Ennis, M. *et al.*, in press).

p0335 Electrical activation of NBD has been reported to depress (Nickell, W. T. and Shipley, M. T., 1988) or to increase (Kunze, W. A. A. *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, W. T. and Shipley, M. T., 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 LOT-evoked field potentials recorded in the GCL. This effect was attributed to muscarinic receptor-mediated inhibition of GABA release from GCs (Elaagouby, A. *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, P. E. *et al.*, 1999). In slices, muscarinic receptor agonists inhibited GCs (Castillo, P. E. *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, P. E. *et al.*, 1999). The morphological identity of these cells is unclear. Behaviorally, muscarinic receptor antagonists impair discrimination among closely related odors (Fletcher, M. L. and Wilson, D. A., 2002).

s0275 ### 2.44.10.2 Noradrenergic Input to MOB

p0340 A significant modulatory input to the bulb is from the pontine nucleus locus coeruleus (LC). In the rat, all LC neurons contain the neurotransmitter, 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 1600 LC neurons) project to the bulb in the rat (Shipley, M. T. *et al.*, 1985). A subset of LC neurons projecting to MOB contain NPY (Bouna, S. *et al.*, 1994). LC axons project mainly to the subglomerular layers of the bulb, particularly in the IPL and GCL (McLean, J. H., *et al.*, 1989). The EPL and MCL are moderately innervated, while the GL is nearly devoid of NE input. NE receptors occur in multiple layers of the MOB and are expressed by multiple cell types, in general consistent with the pattern of NE fiber innervation (for review, see Ennis, M. *et al.*, in press).

p0345 While 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, H. *et al.*, 1987). A subsequent study reported AU38 AU39 that LC stimulation initially decreased and then subsequently increased paired-pulse depression of GC field potential responses to LOT stimulation (Okutani, F. *et al.*, 1998). These effects were attributed to activation of $\beta$ 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. Mitral cell responses to antidromic shocks were not affected, suggesting that NE excites GCs (Mouly, A. M. *et al.*, 1995). In neonatal animals, $\beta$ receptor stimulation in MOB decreased LOT-evoked, paired-pulse inhibition of GC field potentials (Wilson, D. A. and Leon, M. 1988). It is unclear if this was mediated by presynaptic inhibition of transmitter release from MCs and/or increased excitability of GCs.

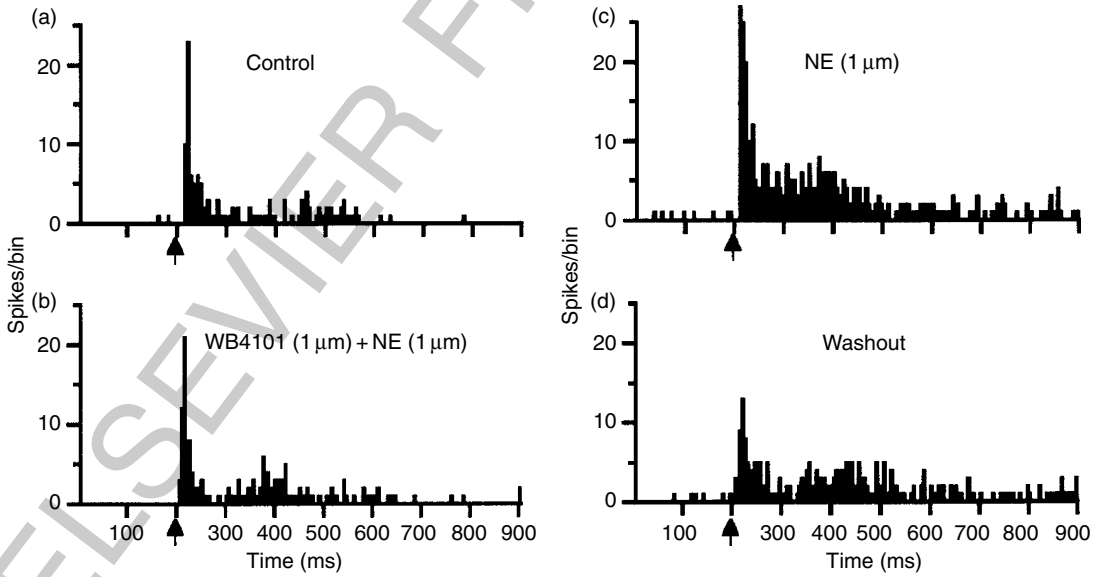
p0350 Cellular recording studies are also somewhat discrepant. In the rabbit and cat, Salmoiraghi *et al.* (1964) AU40 AU41 and McLennan (1971) found that iontophoretically AU42 AU43 applied NE inhibited mitral cells. This effect was blocked by the $GABA_A$ receptor antagonist, bicuculline. In the isolated turtle bulb (Jahr, C. E. and Nicoll, R. A., 1982), mitral cell activity increased following bath application of NE, an effect blocked by bicuculline. In dissociated MOB cultures, NE decreased mitral to granule dendrodendritic synaptic transmission by acting presynaptically at $\alpha 2$ receptors to decrease $Ca^{2+}$ currents in both granule and mitral cells (Trombley, P. Q., 1992; Trombley, P. Q. and Shepherd, G. M., 1992).

p0355 NE release or NE agonists have more consistent effects on ON-evoked responses in mitral cells. 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, M. R. *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, M. M. *et al.*, 1999). Consistent with these *in vivo* findings, application of NE or $\alpha 1$ receptor agonists, but not $\alpha 2$ or $\beta$-receptor agonists, selectively increased mitral cell responses to perithreshold

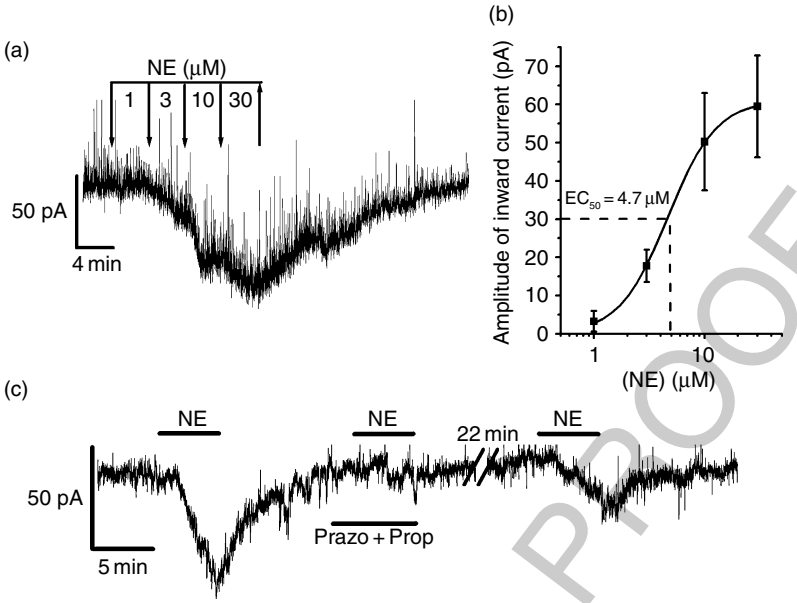
intensity ON stimulation in rat MOB slices (Figure 15) (Ciombor, K. J. *et al.*, 1999). Noradrenergic agonists were without effect on ON-evoked field potentials recorded in the GL, or on ON-evoked postsynaptic currents in mitral cells (Hayar, A. *et al.*, 2001). This suggests that NE-evoked modulation 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 (Figure 16). 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.

p0360 NE inputs to the bulb are critical to olfactory function. Olfactory cues increase the discharge of LC neurons in behaving animals (Aston-Jones, G. and Bloom, F. E., 1981) and trigger rapid increases in NE levels in the MOB (Chanse, N. T. and Kopin, I. J., 1968; Rosser, A. E. and Keverne, E. B., 1985; Brennan, P. *et al.*, 1990). LC projections to the main and accessory olfactory bulb are pivotal to the formation of and/or recall of specific olfactory memories, pheromonal regulation of pregnancy and post-partum maternal behavior (Kaba, H. and Keverne, E. B., 1988; Brennan, P. *et al.*, 1990; Kendrick, K. M. *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, H. and Keverne, E. B., 1989). Systemic administration of adrenergic receptor antagonists or 6-OHDA lesions, selectively destroying only the NE inputs to the MOB, causes the female to abort when presented with the odor of the impregnating male (Rosser, A. E. and Keverne, E. B., 1985; Kaba, H. and Keverne, E. B., 1988; Brennan, P. *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, R. M. *et al.*, 1989). The conditioned preference is associated with odor-specific metabolic changes in the bulb (Coopersmith, R. and Leon, M., 1984).






f0075 **Figure 15** The $\alpha 1$ receptor antagonist WB-4101 prevents norepinephrine (NE)-induced facilitation of mitral cell excitatory responses to perithreshold intensity olfactory nerve (ON) stimulation. (a–d) Peri-stimulus time histograms (PSTHs) showing responses of a mitral cell to perithreshold intensity ON shocks (12 μA, at arrows). (a and b) In the presence of WB-4101 (1 μM), superfusion of NE (1 μM) did not alter (103% of control) the early excitation elicited by ON stimulation. (c) After washout of WB-4101, NE substantially increased (184% of control) the early excitatory response component. (d) The facilitation of the early excitation recovered by 53 min after washout of NE. All PSTHs were generated for 50 consecutive ON shocks. Reprinted from K. Ciombor *et al.*, 1999, Neuroscience, 90, 595–606, with permission from Elsevier, Ltd.




f0080 **Figure 16** Effect of norepinephrine (NE) in voltage-clamp recordings from mitral cells. (a) Inward currents evoked by NE at different concentrations (1, 3, 10, and 30 μM added cumulatively, 4 min at each concentration). (b) A sigmoidal curve was fitted to the NE concentration–response data obtained from four cells. The holding potential was −60 mV. (c) The response to a second application of NE (30 μM) was blocked in the presence of the alpha 1 receptor antagonist prazosin (Prazo; 1 μM) and the beta receptor antagonist propranolol (Prop; 10 μM). The NE-induced inward current recovered partially after washout of the antagonists (about 30 min). Reprinted from Hayar, A. *et al.*, 2001, J. Neurophysiol. 86, 2173–2182, with permission from The American Physiological Society.

Following the conditioning, there is an increased inhibition of mitral cells by the odor (Sullivan, R. M. *et al.*, 1989). Such conditioning is abolished by eliminating NE input to the bulb or via $\beta$-receptor antagonists (Sullivan, R. M. *et al.*, 1989; Wilson, D. A. and Sullivan, R. M., 1991; Sullivan, R. M. *et al.*, 1992; 2000; Moriceau, S. and Sullivan, R. M., 2004). Recent studies from McLean's laboratory demonstrate that this $\beta$-receptor-dependent neonatal learning involves activation of intracellular cAMP AU47 and CREB pathways (Yuan, Q. *et al.*, 2003; McLean, J. H. and Harley, C. W., 2004).

s0280 **2.44.10.3 Serotonergic (5-HT) Input to MOB**

p0365 The midbrain dorsal and median raphe provides strong serotonergic inputs to the MOB. In the rat, about 1000 dorsal and 300 median raphe neurons project to the bulb (McLean, J. H. and Shipley, M. T., 1987a; 1987b). 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. 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, while thinner serotonergic axons preferentially innervate inframitral layers (McLean, J. H. and Shipley, M. T., 1987a; 1987b). In neocortex, thick axons arise from the median raphe and thin axons arise from dorsal raphe (McLean, J. H. and Shipley, M. T., 1987a; 1987b), 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 (for review, see Ennis, M. *et al.*, in press).

In the GL, it was recently reported that 5-HT p0370 depolarized 34% of JG cells *in vitro* via activation of $5HT_{2C}$ receptors (Hardy, A. *et al.*, 2005). The 5-HT-induced depolarization was due to activation of a nonselective cation current with a reversal potential of −44 mV. The heterogeneous electrophysiological properties of 5-HT-responsive JG cells suggested that several types of JG cells could be targeted by 5-HT centrifugal fibers. A subset of mitral cells was also depolarized by 5-HT acting at $5\text{-}HT_{2A}$ receptors. By contrast with these results, another subset of mitral cells was hyperpolarized by 5-HT, an action that was indirectly mediated by GCs as it was blocked by $GABA_A$ receptor antagonists (Hardy, A. *et al.*, 2005). This effect of 5-HT was also thought to

be mediated by 5-$HT_{2A}$ receptors. Behavioral studies indicate that lesion of serotonergic fibers reversed conditioned olfactory learning (Morizumi, T. *et al.*, 1994) and also induced glomerular atrophy. Behavioral work on neonates by McLean (McLean, J. H. *et al.*, 1996) showed that 5-HT depletion or 5-$HT_2$ receptor antagonism compromised olfactory learning and that 5-HT release or 5-$HT_2$ receptor activation promoted odor conditioning. 5-HT release also appears to facilitate $\beta$ receptor-mediated, NE-induced olfactory learning by facilitating cAMP-mediated mechanisms (McLean, J. H. and Harley, C. W., 2004).

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