

Dendritic processing within olfactory bulb circuits

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Odors elicit a well-organized pattern of activation in glomeruli across the surface of the olfactory bulb. However, the mechanisms by which this map is transformed into an odor code by the bulb circuitry remain unclear. Recent physiological studies in bulb slices have identified several synaptic processes that could be involved in sharpening odorant signals. Mitral cells within a single odorant receptor-specific network can be synchronized by dendrodendritic excitatory interactions in a glomerulus, whereas mitral cells in different networks engage in long-lasting lateral inhibition mediated by dendrodendritic synapses with interneurons. The emerging picture is one in which groups of mitral cells use a unique set of mechanisms to accomplish computational functions similar to those performed by analogous modular structures in other sensory systems.

A great deal has been learned recently about how odors are represented in the mammalian olfactory system. Odor stimulation results in activation of patterns of glomeruli distributed across the surface of the main olfactory bulb. However, it is not well understood how these patterns of glomerular activity are transformed by the circuitry of the bulb, or even which are the crucial elements in these circuits. In part, this lack of knowledge reflects the unusual nature of some of the synaptic mechanisms that play a vital part in the circuits of the olfactory bulb. Many neurons in the olfactory bulb communicate via dendrodendritic synapses, and several neuronal types in the main olfactory bulb are known to modulate their own activity through the transmitters that they themselves release [1,2]. Some cell types are also known to release transmitter in an action potential-independent manner [3–5]. How do these unusual synaptic properties influence the function of olfactory bulb circuitry? This article reviews some important recent findings about the circuitry of the olfactory bulb, in particular focusing on how synaptic mechanisms alter the firing of the output neurons of the olfactory bulb, the mitral cells.

Intraglomerular and interglomerular circuits

Olfactory bulb glomeruli are thought to be the functional units of olfactory bulb processing [6]. This designation

reflects both the homogeneity of the sensory inputs received by the cells in a glomerular unit and the degree to which the neurons in the same glomerular unit are interconnected. In each glomerulus the primary dendritic tufts of ~50 mitral and tufted cells receive convergent input from ~5000 axons of olfactory receptor neurons (ORNs), all of which express the same odorant receptor and which should therefore be activated by similar odorants [7,8] (Fig. 1). Because each group of glomerulus-specific mitral and tufted cells is odorant receptor-specific, they form a functionally defined network somewhat analogous to barrels in the somatosensory cortex or to ocular-dominance columns in visual cortex. Anatomical studies have failed to provide any evidence for monosynaptic excitatory connections between mitral cells in mammals [9], as seen in neocortical structures, but there is evidence that glomerulus-specific mitral cells are electrically coupled [10]. These cells are also coupled di-synaptically via inhibitory interneurons. Mitral cells and tufted cells thus provide the output from the olfactory bulb to the rest of the brain.

The activity of mitral and tufted cells is regulated by dendrodendritic synaptic contacts with periglomerular cells and granule cells, which are the two major types of interneurons in the olfactory bulb. Periglomerular cells are a heterogeneous group of neurons that make dendrodendritic synaptic connections with mitral cell and tufted cell primary dendrites in the glomerulus and that include both GABAergic and dopaminergic subtypes. Periglomerular cells also form axodendritic connections outside glomeruli and dendro-axonic synapses onto ORN axons, which they inhibit [11–14]. Granule cells form reciprocal dendrodendritic contacts with mitral cell and tufted cell dendrites and they are believed to be exclusively GABAergic (but see Ref. [15]). Because of the differences in their dendritic arborization and connectivity, one of the main differences between periglomerular and granule cells is that they mediate interactions between anatomically and functionally distinct groups of mitral and tufted cells: periglomerular cell dendrites mediate mostly interactions between cells affiliated with the same glomerulus (intraglomerular interactions), whereas granule cells mostly mediate interactions between mitral and tufted cells projecting to many different glomeruli (interglomerular interactions). The focus of this review is on mechanisms by

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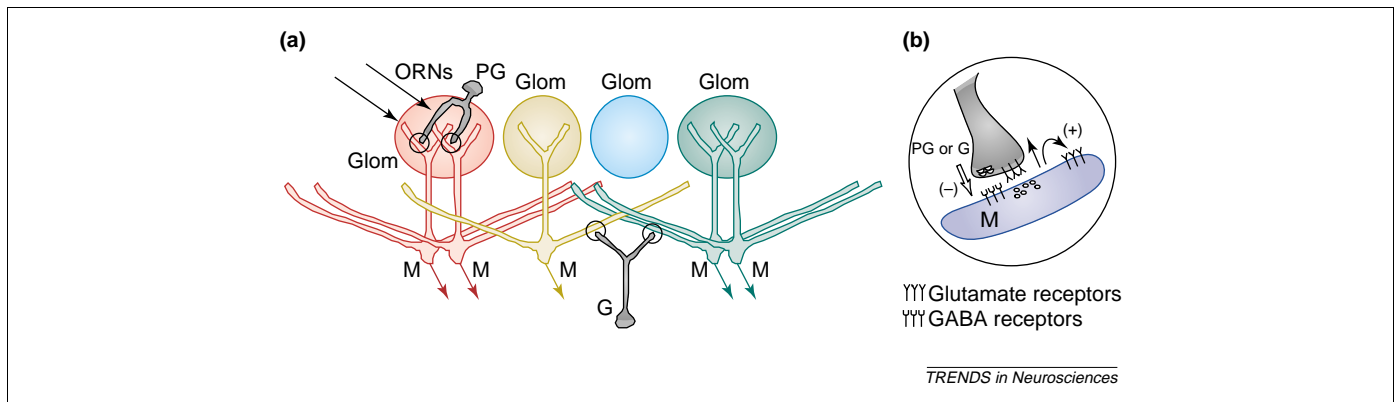


Fig. 1. A simplified circuit of the olfactory bulb. (a) Excitatory mitral cells (M) project their primary dendrites to glomeruli (Glom), where they receive input from the axon terminals of olfactory receptor neurons (ORNs). Mitral cells have been color-coded to indicate that each glomerulus-specific group is associated with a single type of odorant receptor. Arrows emerging out of mitral cell bodies depict axons. Mitral cells also receive dendrodendritic synaptic input (circled) from periglomerular (PG) cells at their primary dendrites within glomeruli and from granule cells (G) at their secondary dendrites. Despite the close apposition of their secondary dendrites, mitral cells are not believed to make direct chemical synaptic contacts with each other. Not shown are axons of periglomerular cells, or several other cell types in the bulb, including tufted cells, that have less well-defined functions. (b) A typical dendrodendritic synapse between a mitral cell (blue) and an interneuron (either a periglomerular or a granule cell; gray). Many mitral-to-periglomerular cell and most mitral-to-granule cell synapses are reciprocal synapses, in which the excitatory mitral-to-interneuron glutamatergic synapse (black straight arrow) is directly adjacent to the interneuron-to-mitral cell GABAergic synapse (white arrow). Glutamate autoreceptors are located near the site of glutamate release on the mitral cell (black curved arrow).

which mitral and tufted cells (especially mitral cells) within these different functional groups interact, either directly or through local circuits with periglomerular and granule cells. Much less is known about the properties of other connections made with and by mitral cells and, thus, these will not be considered here.

What happens after mitral cells receive ORN input? How is ORN activity propagated to other neurons in the bulb, and how is the activity of these neurons influenced by the ongoing activity of neurons in other glomerular units? Several unusual synaptic mechanisms participate in the refinement of odor-evoked activity within and between glomeruli. This review discusses these mechanisms, starting with the most 'local' mechanism, self-excitation in mitral cells, and progressing to excitatory and inhibitory synaptic circuits that operate at a longer range.

Self-excitation and inhibition

The first evidence for self-excitation in mitral cells came from the turtle olfactory bulb, when injection of a depolarizing current into a mitral cell elicited a prominent glutamate receptor-dependent after-depolarization [16]. Based on its insensitivity to blockade of the mitral cell action potential (with tetrodotoxin, TTX), it was suggested that self-excitation originated at dendrodendritic synapses rather than at recurrent axon collaterals. More recent patch-clamp studies in rodent slices have shown that both AMPA and NMDA glutamate receptors can mediate self-excitation [17,18] and, moreover, that such responses occur at both primary and secondary dendrites [17]. Although it has been proposed that a subclass of glutamatergic granule cells can mediate self-excitation of mitral cells [15], the main component of self-excitation is generally believed to result from direct activation of presynaptic dendritic autoreceptors on mitral cells rather than from a polysynaptic path. Such presynaptic autoreceptors have been localized anatomically on mitral cells near dendrodendritic synapses [19], although their exact location with respect to the glutamate release site is not

known [20]. Functionally, self-excitation can drive an after-discharge in mitral cells that can last for hundreds of milliseconds [16,17,21], reflecting the fact that a significant component of the response is mediated by kinetically slow NMDA autoreceptors.

In addition to self-excitation, mitral cells can undergo self-inhibition in response to depolarization [3–5,22–24]. This inhibition, which is insensitive to TTX, reflects the activation of interneurons by glutamate released from the mitral cell dendrite, which in turn leads to GABA release back onto the mitral cell. Because granule cells outnumber periglomerular cells, it is generally assumed that most of the inhibition is derived from the former [7]. Interestingly, self-inhibition is nearly abolished by the NMDA receptor antagonist DL-AP5 [4–5]. This observation implies that the activation of granule cells at dendrodendritic synapses depends on NMDA receptors, in contrast to synapses elsewhere in the brain, where AMPA receptors generally drive action potential firing. Because most dendrodendritic synapses are reciprocal, one explanation for the NMDA receptor-dependence of inhibition is that GABA release is driven locally by Ca^{2+} permeating NMDA receptors [25]. NMDA receptors also appear to be more effective than AMPA receptors at driving local depolarizations that open voltage-gated Ca^{2+} channels [26–28]. From a functional perspective, the main impact of the NMDA receptor-dependence of granule cell activation is that GABA release from granule cells occurs as a long-lasting barrage. The resulting self-inhibitory response lasts for hundreds of milliseconds [3–5,22–24], similar to the duration of self-excitation. Moreover, the dependence on NMDA receptor activation suggests that GABA release from granule cells might be favored by near coincident inputs to granule cells.

If mitral cells can undergo both self-excitation and self-inhibition, which signal is stronger? Both types of signals have been reported to have amplitudes of several millivolts in published studies, but many of these have used manipulations, such as the removal of Mg^{2+} from the bath, to enhance the signals. The actual amplitudes of

self-excitation and inhibition during odor responses *in vivo* will depend on the activation states of the mitral cell and the network of granule cells [24].

Intraglomerular excitation and inhibition

Recent physiological experiments have shown that activation of mitral cells also causes intraglomerular excitation [1,10,18,29–30] (Fig. 2a). Paired mitral cell recordings have shown that this excitatory coupling coexists with intraglomerular inhibition (Fig. 3b), but that the excitation is larger than inhibition and that excitation and inhibition have different time scales [30]. Intraglomerular excitation in response to stimulation of a single mitral cell is observed in all pairs that have primary dendritic tufts that terminate in the same glomerulus, and is mediated primarily by AMPA receptors, at least under physiological recording conditions [10,30]. This connectivity is strong, with a single action potential in a mitral cell associated with a given glomerulus causing an average depolarization of ~ 1 mV in the other mitral cells in that glomerulus. Additionally, olfactory nerve stimulation can result in the all-or-none activation of the entire set of mitral cells associated with a given glomerulus [18,29]. These synchronized network depolarizations are large (5–10 mV), long-lasting (duration >100 ms) and mediated primarily by NMDA receptors.

Despite the physiological observation of mitral–mitral excitatory coupling, the absence of anatomical evidence for monosynaptic connections between mitral cells makes the mechanism of intraglomerular excitatory coupling somewhat unclear. Two mechanisms have been proposed for this coupling: (1) direct spillover of glutamate from dendritic release sites of one mitral cell onto glutamate receptors of the second mitral cell [30], and (2) activation of glutamate autoreceptors on the mitral cell that is firing action potentials, which in turn causes a depolarization in the second mitral cell through gap-junction-mediated coupling of the autoreceptor potential [10] (Fig. 2b). Functionally, the AMPA receptor-mediated signals seen between pairs of mitral cells can mediate synchronized spiking in glomerulus-specific mitral cells (Fig. 3a), whereas the slow synchronized network depolarizations

might be involved in tuning mitral cell responses to the breathing cycle [18].

Intraglomerular inhibition (Fig. 3b) probably results from activation of both periglomerular and granule cells. Mitral–periglomerular dendrodendritic synapses are often assumed to function in a manner similar to mitral–granule synapses; however, the diversity of periglomerular cell types and the presence of various neuromodulators in these cells suggests that the details might be substantially more complicated. Based on the connectivity, inhibition from periglomerular cells could differ functionally from granule cell inhibition, in that periglomerular cell inhibition might prevent activity and glutamate release from the mitral cell tuft and, thus, regulate intraglomerular excitation. Granule cell inhibition might be more adapted to regulating the mitral cell axonal output and also action potential propagation in mitral cell lateral dendrites [31,32].

Interglomerular circuits

The activity of mitral cells in a particular glomerular unit also is influenced by the activity of mitral cells associated with other glomeruli. The main such interglomerular circuit involves the activation of granule cells by glutamate released from mitral cell dendrites. These cells in turn release GABA onto mitral cell somata and dendrites, inhibiting mitral cell activity. The mechanisms underlying lateral inhibition of mitral cells by granule cells are thought to be similar to self-inhibition, as described in the section on self-excitation and inhibition. This claim is supported by the observations that lateral inhibition is highly sensitive to blockade of NMDA receptors and can be observed in the presence of TTX, indicating that it does not require Na^+ spikes in granule cells [1]. The importance of this independence of granule cell GABA release on Na^+ spikes is unclear. *In vivo*, granule cells do fire action potentials in response to odor stimulation [33–35], suggesting that granule cell-mediated inhibition of mitral cells could proceed by two different mechanisms. Synaptic activation of local domains of the granule cell dendritic tree might lead to GABA release from small subsets of granule cell spines [36]. If this release does not require an

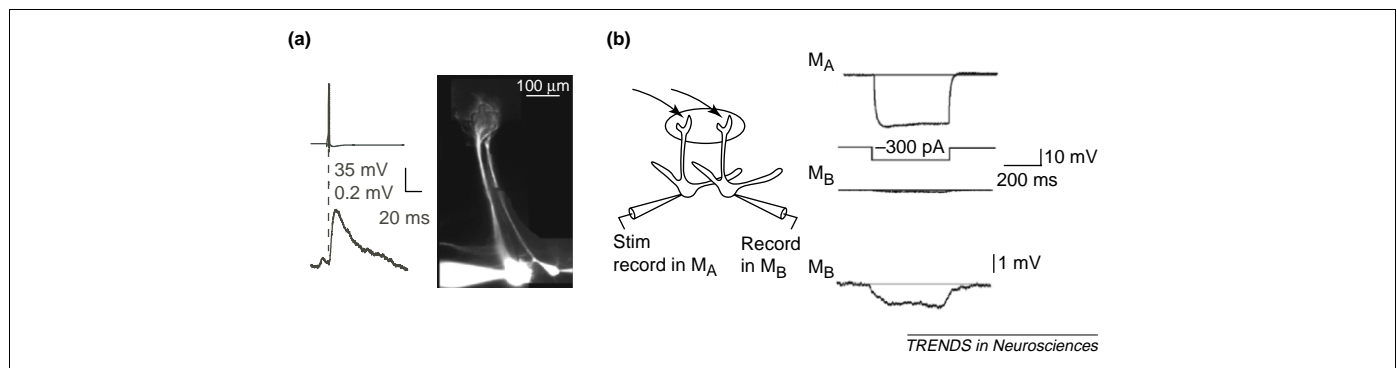


Fig. 2. Mechanisms of intraglomerular coupling between mitral cells. Mitral cells in the same glomerular network are coupled by an AMPA receptor-dependent fast synaptic mechanism and also by electrical synapses. (a) A single action potential elicits fast AMPA receptor-dependent excitatory coupling between mitral cells that have apical dendrites in the same glomerulus. These events, which are recorded at the mitral cell soma, have an average amplitude of ~ 1 mV and are likely to provide an important mechanism for coupling the activity of mitral cells in the same glomerular network. (b) Mitral cells in the same glomerular network (M_A and M_B) are electrically coupled, as evidenced by a small ~ 1 mV hyperpolarization that appears in M_B following a hyperpolarizing current injection into M_A (the trace from M_B is shown at two different voltage-amplitude scales). This electrical coupling could mediate the AMPA receptor-dependent coupling shown in (a) following activation of AMPA autoreceptors on the active mitral cell. Reproduced, with permission, from Ref. [10], © (2002) Nature Publishing Group (<http://www.nature.com/>), and from Ref. [30].

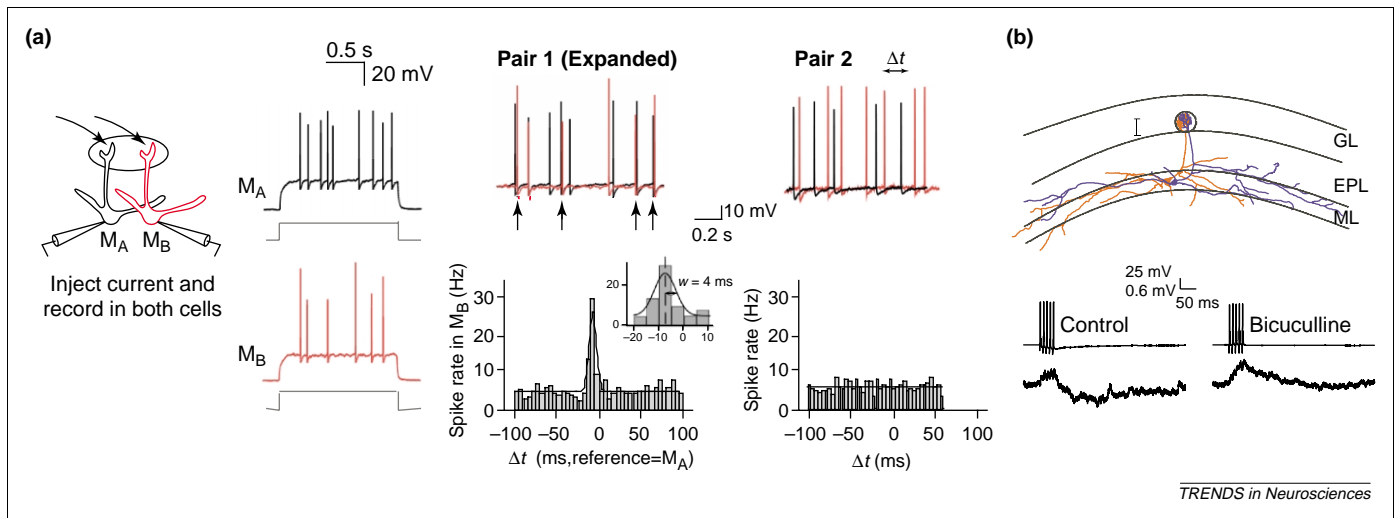


Fig. 3. Functional role of intraglomerular mitral cell coupling. (a) Mitral cells associated with the same glomerulus excited to near threshold show highly synchronized action potential firing. Voltage traces from two mitral cells (M_A and M_B ; pair 1) show spiking in response to current injection. Expanded and superimposed traces show that many of the action potentials in the two cells occur in an almost synchronized fashion (arrows). Cross correlograms shows that the synchronization of firing is very precise [4 ms width (w) of a Gaussian fit, as shown in inset]. Cells in different glomerular networks showed no correlated spiking (pair 2). Mitral cells in the same glomerular network also are coupled by inhibition, which might be mediated by granule cells, periglomerular cells, or both. (b) Reconstruction of two mitral cells having apical dendrites in the same glomerulus. Traces below show that, under control conditions, a train of five action potentials in one cell results in an initial depolarization, followed by a long-lasting hyperpolarization. This hyperpolarization is blocked by the GABA_A receptor antagonist bicuculline. Similar to interglomerular lateral inhibition, intraglomerular inhibition has a slower time course than the AMPA receptor-dependent fast excitatory coupling. Abbreviations: EPL, external plexiform layer; GL, glomerular layer; ML, mitral cell layer. Reproduced, with permission, from Ref. [10], © (2002) Nature Publishing Group (<http://www.nature.com/>), and from Ref. [30].

all-or-none event such as an action potential, then it could represent a form of graded synaptic transmission. By contrast, action potential firing in granule cells might result in global elevation of Ca^{2+} levels and the release of GABA from hundreds of granule cell spines. Although such a model is interesting, in that it would allow for exquisite control of inhibition as a function of local input, further experimental evidence of spatially specific activation of granule cell dendritic arbors needs to be provided.

Kinetically, lateral inhibition is slow, both in rise and in decay time [1,30]. The kinetics of lateral inhibition are not, however, due to dependence on intrinsically slow GABA_B receptors. Rather, similar to self-inhibition, lateral inhibition is slow because it is mediated by a long-lasting increase in the frequency of GABA release. Whether this process reflects slow, asynchronous activation of a large number of granule cells, each of which then releases GABA in a phasic manner, or reflects asynchronous release from individual granule cell spines, perhaps due to prolonged elevation of Ca^{2+} levels or prolonged depolarization, is not known. The lateral inhibitory signal recorded in physiological concentrations of Mg^{2+} is small, with inhibitory postsynaptic potentials (IPSPs) elicited by trains of ten action potentials (at 100 Hz) having a peak amplitude of <0.5 mV [30]. In many cases, single action potentials elicit no measurable response at all, although short bursts of action potentials show that the two mitral cells are indeed coupled by lateral inhibition. This observation highlights the cooperative nature of granule cell-mediated lateral inhibition.

Impact of olfactory bulb circuitry on odor coding

The odor code begins in the olfactory bulb as a map of glomerular activation, with each glomerulus reflecting one activated odorant receptor class [37,38]. It has been widely suggested that the function of the bulb is to sharpen the

odor code through lateral inhibition between different odorant receptor-specific networks of mitral cells [35,39] (see also Ref. [40] for discussion of the insect olfactory system). We favor a modified model of lateral interactions that incorporates excitation as much as inhibition (Fig. 4),

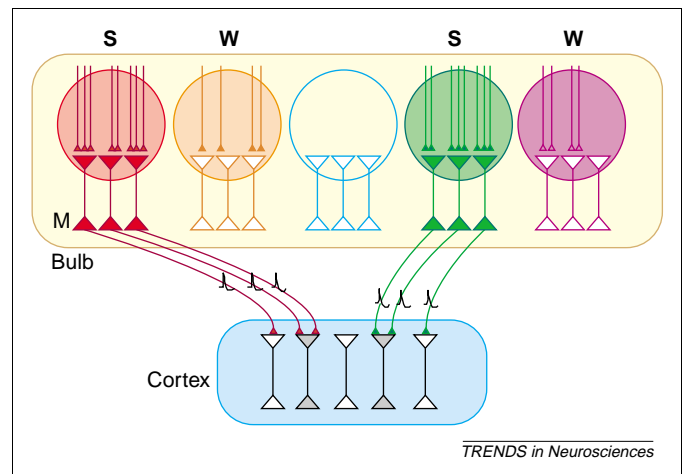


Fig. 4. Intraglomerular excitation and interglomerular lateral inhibition sharpen the odor code. A simplified olfactory network that includes an olfactory bulb with five glomeruli corresponding to five different odorant receptors (color-coded); each glomerulus has three affiliated mitral cells (M). In this example, a hypothetical odor strongly activates (S) red and green glomeruli and weakly activates (W) orange and purple glomeruli. The activation of each mitral cell (shown as filled triangles) depends on whether its associated network undergoes an all-or-none slow depolarization. Because the probability of this depolarization is determined by the strength of input from olfactory receptor neurons and lateral inhibition from other mitral cell networks through granule cells (not shown), networks associated with strongly activated glomeruli are favored. The net effect is a reduction in the number of mitral cell networks activated (two) as compared with activated glomeruli (four), but all mitral cells within an activated network are active. Rapid intraglomerular excitation further amplifies strongly activated networks by driving synchronized spikes. Spike synchronization contributes to excitatory postsynaptic potential (EPSP) summation and activation of postsynaptic cortical neurons in the olfactory cortex that receive input from more than one glomerulus-specific mitral cell (bottom; shown as gray-filled neurons). Only axons of activated mitral cells are depicted.

with the key elements being the slow, 5–10 mV intraglomerular depolarizations and interglomerular lateral inhibition. Because the probability of slow depolarization is determined by the strength of input from ORNs and the lateral inhibition between networks, antagonism between the two would favor networks affiliated with strongly activated odorant receptors. This model deviates from traditional views of lateral inhibition in that mitral cell spiking requires the large-amplitude depolarization. Moreover, because slow excitation is an all-or-none event, antagonism between excitation and inhibition will result in a reformatting of the odor code, from a range of graded responses among many different odorant receptors to a reduced map of mitral cell activity comprising a smaller number of highly active networks.

The ~1 mV AMPA receptor-mediated excitatory signals seen between pairs of glomerulus-specific mitral cells are likely to have a different function. These relatively rapid signals, which persist for 10–20 ms, could result in synchronized spikes in mitral cells associated with strongly activated odorant receptors and, thus, increase their effective weight at synapses downstream in the olfactory cortex. Rapid intraglomerular excitation could work in conjunction with the larger and slower intraglomerular excitatory signals, as the latter provides the template on top of which the rapid depolarizations drive synchronized spikes. Indeed, the slow depolarizations, which are synchronized for glomerulus-specific mitral cells, might be required to remove possible desynchronizing influences of ORN inputs, which could obscure the rapid synchronized depolarizations.

Based on studies in the insect olfactory system, it has been suggested that odor discrimination relies on the synchronization of olfactory neuron spiking by inhibitory networks [41]. However, the actual function of such synchronization remains unproven. For example, the main evidence for this model is that GABA receptor antagonists, which block synchronized activity in insects, interfere with odor discrimination [42]; however, blockade of inhibition is expected to cause many changes in olfactory network activity, including changes in lateral inhibition. An additional crucial question is whether inhibitory interneurons are even capable of driving the rapid spike synchronization on which this model depends. In general, interneuron networks will only be effective in synchronizing spiking when inhibition is fast because, under these conditions, neurons will recover from inhibition within the same narrow time window. In mammals, the available data from slices are inconsistent with interneuron networks in the bulb meeting this requirement. Although spontaneous IPSPs in mitral cells can be rapid [43], self-inhibitory and lateral-inhibitory responses to mitral cell stimulation persist for hundreds of milliseconds. It remains to be seen whether inhibition is fast enough to synchronize mitral cell spiking under certain conditions *in vivo* in mammals [44], or whether there are differences in the properties of inhibitory interneurons in insects versus mammals. Slow inhibition in the mammalian olfactory bulb might instead function to synchronize mitral cell networks on a slow timescale [45] or contribute

to dynamic, slow changes in odor-evoked mitral cell activity patterns [35,46].

Concluding remarks

In many sensory systems, including the olfactory bulb, rodent barrel cortex and primary visual cortex, inputs and local circuitry are organized in modular fashion – with similar inputs being received by groups of cells that are highly interconnected. This modular organization offers several interesting functional possibilities. Strong excitatory connections within a sensory module can serve to reinforce the activity of cells in the module, leading to effective ‘all-or-none’ activation of the cells representing a particular stimulus. Such amplification might be important for making the sensory system more sensitive to its preferred stimulus. However, if the responses of all cells in the same sensory module are the same, this would lead to a massive redundancy that would decrease the ability of the sensory system to represent many different stimuli. This problem of balancing sensitivity and dynamic range is probably solved multiple times in each sensory system. The further elucidation of olfactory circuitry might provide insights into how the appropriate balance is achieved by the unusual synaptic mechanisms of the olfactory bulb.

Many other unanswered questions remain about the functions of olfactory bulb circuitry. One set of crucial issues concerns the relationship between the olfactory bulb circuitry and the observed activity of olfactory bulb neurons *in vivo*. Odors induce oscillations in the bulb [47–49], most notably those occurring at 40 Hz and near the respiration frequency (2–8 Hz). Some of these patterns are driven by ORN input [34] but others can be generated by the circuitry intrinsic to the bulb. Future studies on the mechanisms of lateral inhibition and excitation will begin to address how these circuits participate in the generation of these oscillations. Short-term plasticity of bulb connections is likely to be crucial to understanding the waxing and waning of these oscillations that occurs over the time course of odor stimulation. An additional issue related to the function of inhibitory networks is the relative impact of local, graded release of GABA, versus that of action potential-evoked release, on mitral cell activity. Further work also is needed on how feedback from the olfactory cortex influences olfactory bulb circuits, as these inputs certainly will be crucial in determining the odor-evoked activity of olfactory bulb neurons.

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