serve both as enhancer or repressor depending on whether its binding sites are positioned up- or downstream of the target exon—an example of bidirectional regulation at the level of RNA processing.

Alternative pre-mRNA splicing events are predicted to occur in ~95% of multi-exon human genes. Neurons use alternative splicing extensively to tailor protein activity profiles to optimize neuronal tasks and to adapt to physiological demands. Coordinated alternative pre-mRNA splicing across functionally related genes offers a mechanism for cells to orchestrate changes in ion channels to achieve balance. Future studies aimed at identifying cell-specific and activity-dependent splicing factors that coordinate Trip8b exon inclusion and repression could show if and how neuronal excitability is controlled at the molecular level. Furthermore, once the splicing factors are known, their levels could be manipulated to induce changes in the abundance of specific *Trip8b* isoforms to assess their influence on HCN channel activity in neurons.

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Inhibition Acts Globally to Shape Olfactory Cortical Tuning

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Lateral inhibition between near-neighbor neurons has long been thought to be important for narrowing the receptive fields of neurons in many sensory systems. A new study by Poo and Isaacson in this issue of *Neuron* examining olfactory processing finds that "global" inhibition within the primary olfactory cortex might accomplish a similar end.

Within many sensory systems, broadly tuned lateral inhibition has commonly been proposed to narrow the receptive fields of neurons, a function that could be important for contrast enhancement. This mechanism however has come under some question in recent years, based on experiments in which inhibitory and excitatory synaptic activity has been directly recorded in neurons in vivo. Inhibition and excitation in fact often appear to be "balanced," meaning that inhibition is no more ubiquitous or broadly tuned to different stimuli than excitation is. Balanced inhibition and excitation is observed in the primary sensory cortices involved in visual, auditory, and somatosensory processing (Anderson et al., 2000; Wehr and Zador, 2003; Tan et al., 2004; Wilent and Contreras, 2005; Priebe and Ferster, 2008), all structures where lateral inhibition has been thought to have important functions.

Within this issue of *Neuron*, Poo and Isaacson (2009) provide interesting experimental results to add to the discussion, based on their in vivo patch-clamp recordings of synaptic activity within the primary olfactory cortex, specifically the anterior piriform cortex, which is the structure that receives the most direct inputs from olfactory bulb mitral cells. Their basic strategy, analogous to what has been used in studies in other sensory systems, was to record inhibitory and excitatory postsynaptic currents (IPSCs and EPSCs, respectively) in pyramidal cells (PCs) in response to a small panel of monomolecular odors. From these recordings, they derived estimates both of how responsive the synaptic activity of a single PC was to the panel of odors, and of how responsive

the population of PCs was to any one odor. In addition to synaptic activity, they also measured action potential firing ("spiking") in the PCs for comparison, in this case using cell-attached patch-clamp recordings. Their use of cell-attached recordings to measure spiking was notable in that, unlike conventional microelectrode methods that can overreport the activity of responsive cells, this method provided an unbiased way to assess how often PCs spiked.

What they found was quite striking. The excitatory synaptic events and spiking in PCs both appeared to be quite narrowly tuned to the odors, usually responding to zero or only one of four odors that comprised their main test panel. Inhibition, in contrast, responded much more broadly, with the majority of PCs showing evoked IPSCs in response to three or all four of the odors tested. In addition, single odors evoked spikes and EPSCs in only 10% and 20% of the cells, respectively, with most evoked spike responses being very weak, whereas IPSCs were observed in ~50% of the PCs. That inhibition in PCs happens much more often than excitation was further supported when they found high rates of odor-evoked excitatory responses in identified GABAergic interneurons. These results suggested that inhibition is broadly tuned and ubiquitous in the primary olfactory cortex, whereas excitation is narrowly tuned and relatively unusual, i.e., "sparse."

These results showing unbalanced inhibition and excitation fit with the predictions of classical models of receptive field-tuning by lateral inhibition, but does such a phenomenon occur within the primary olfactory cortex? The answer is that it probably does not, at least not in the manner proposed for circuits in other sensory systems. A key common feature of primary cortices in other sensory systems is that the neurons are ordered by functional type. Neurons with the same function are grouped together (e.g., in barrels in the somatosensory cortex), while neurons of similar but nonidentical function are near-neighbors. However, within the primary olfactory cortex, it is quite unlikely that such ordering of neurons exists. While bulb mitral cells that provide the input into the cortex are themselves ordered functionally, by odorant receptor (OR)-type, the results of tracer studies in these cells suggest that any spatial specificity by functional type is likely not preserved in the olfactory cortex (Neville and Haberly, 2004). Also, it is very unlikely that there is any near-neighbor ordering of neurons by similarities in functional type in the olfactory cortex (chemotopy), given that there appears to be little chemotopy within the upstream olfactory bulb (Soucy et al., 2009). These considerations would suggest that the form of lateral inhibition within the olfactory cortex would be fundamentally different from what is generally discussed for other sensory systems, being much more broadly distributed. Poo and Isaacson (2009) call the inhibition they observe in their study "global," based on their observations that odors activated inhibitory synaptic activity in many different PCs, and also because both preferred and nonpreferred odors (in terms of excitation) resulted in similar magnitudes of inhibition.

What type of neuronal circuit would be capable of producing global inhibition? Part of the answer to this question came from further experiments that Poo and Isaacson (2009) performed in which they measured EPSCs and IPSCs in PCs in response to electrical stimulation of axons of mitral cells in the lateral olfactory tract. In these studies, they found that weak stimulation activated IPSCs with a higher probability than EPSCs, based upon which they reasoned that interneurons receive more convergent inputs of mitral cell axons than PCs. The most explicit form of this model is illustrated in Figure 1A, which shows a PC, along with a connecting interneuron that receives converging inputs from multiple mitral cells. The model also shows the interneuron receiving inputs from mitral cells of differing OR-specificities, to account for the fact that there likely is little spatial ordering of neurons by functional type (see above). Because the interneuron receives more mitral cell inputs of a wider range of OR-specificities as compared to PCs, this scheme would account for the experimental observations that an odor-activated inhibition in PCs occurs much more often than excitation, and also that inhibition was much more broadly tuned to different odors. There are of course other schemes compatible with their data, for example the model in Figure 1B that has similar convergence levels of mitral cell axons onto single PCs and interneurons, but has multiple interneurons targeting a PC. The differences in these schemes are less important than what they have in common, which is that the local inhibitory circuit, whatever its composition, receives more mitral cell inputs than PCs.

Among the issues to be addressed by future studies is what the function is for global inhibition. One obvious function is not so different from that proposed for the "classical," local form of lateral inhibition in other sensory systems; that is, to narrow the receptive field of excitation in neurons. In fact, Poo and Isaacson (2009) propose something like that function to account for the large differences in odor-tuning that they observed for inhibition versus excitation in PCs. The mechanics of how that narrowing could be achieved are unique: instead of having strongly activated neurons suppress neighboring, weakly activated neurons through local interactions, global inhibition would suppress excitation in PCs throughout the olfactory cortex, with the only excited PCs being those that receive the strongest excitatory inputs from mitral cells. Demonstrating that global inhibition is actually the cause of the narrowing tuning of excitation in PCs will not be trivial. An obvious strategy would be to show that the odor "tuning curve" for excitation in PCs broadens when inhibition is blocked pharmacologically or with genetic manipulations. However, such experiments can be difficult to interpret, since blocking inhibition can cause brain circuits to enter into epileptic states that cannot be easily compared to nonblocked states.

There are also other possible functions to consider. For example, it has long been known that odors evoke strongly synchronized activity within the olfactory bulb (Adrian, 1950), and it appears that this synchronization can extend to mitral cells that code for different ORs (Kashiwadani et al., 1999). Strong global inhibition could help ensure that the piriform cortex responds selectively to synchronized mitral cell inputs, since these inputs would be the only ones that could summate and drive PCs past spike threshold. A situation in which global inhibition facilitates preferential selection of synchronized signals of differing OR-specificities is especially

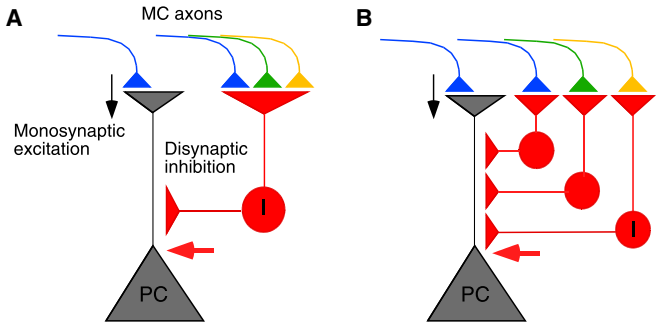

Figure 1. Two Circuits that Can Account for Global Inhibition and Sparse Excitation in the Primary Olfactory Cortex

(A) A pyramidal cell (PC) receives input from a GABAergic interneuron (I) that is part of a feedforward inhibitory path. In this example, there are more convergent mitral cell (MC) excitatory inputs onto the interneuron than onto the PC. Thus, in recordings of PCs, disynaptic inhibition (MC-to-I-to-PC) dominates over monosynaptic excitation (MC-to-PC) upon stimulation of MC axons. MC axons are color-coded to indicate differing odorant receptor (OR)-specificities.

(B) Disynaptic inhibition can also dominate over monosynaptic excitation if there are many interneurons that synapse onto the PC. In this scheme, the convergence of MC axons onto any one interneuron is similar to the PC.

attractive for considering the behavior of PCs, in light of evidence that PCs can integrate information contained across different components of an odor (Zou and Buck, 2006). It is also possible that the function of global inhibition has strictly to do with the sparse neural excitation that may result from global inhibition. Sparse neural coding has been observed in brain regions associated with different sensory systems, including olfaction (Perez-Orive et al., 2002; Olshausen and Field, 2004; Rinberg et al., 2006; Davison and Katz, 2007), and there are several often-cited possible advantages in terms of metabolic efficiency, computational ease, and learning.

A final issue to raise, at least as fundamental as these functional issues, is, how general the findings of Poo and Isaacson (2009) are that inhibition is global and excitation sparse in the primary olfactory cortex. Their experiments were done in anesthetized animals, which is what permitted them to perform the careful analysis of synaptic activity and spiking in PCs. However, what happens in an awake and behaving animal? Excitatory odor representations in the olfactory bulb appear to be more sparse in awake, behaving as compared to anesthetized animals (Rinberg et al., 2006), yet this tendency may not necessarily extend to the piriform cortex, owing to its extensive intracortical associative and neuromodulatory connections. Another issue is that Poo and Isaacson (2009) used simple monomolecular odors in their studies, which leads to the question of what happens when an animal is exposed to more complex natural odors. If PCs are integrators of information associated with different components of an odor, it is possible that natural odors that activate more different types of ORs, and thus potentially more mitral cells, will lead to broader excitation in PCs. On the other hand, one can easily imagine that the magnitude of global inhibition within the olfactory cortex would scale with the amount of mitral cell input. Complex natural odors thus might enhance inhibition in such a way that activity will be lost in those PCs that respond to the monomolecular components alone, and result in new activity only in the select PCs that integrate all components of the odor. Hence, the basic pattern of global inhibition and sparse excitation seen for simple odors might be retained for natural odors.

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