PERSPECTIVES: NEUROBIOLOGY

Sniffing Out Odors with Multiple Dendrites

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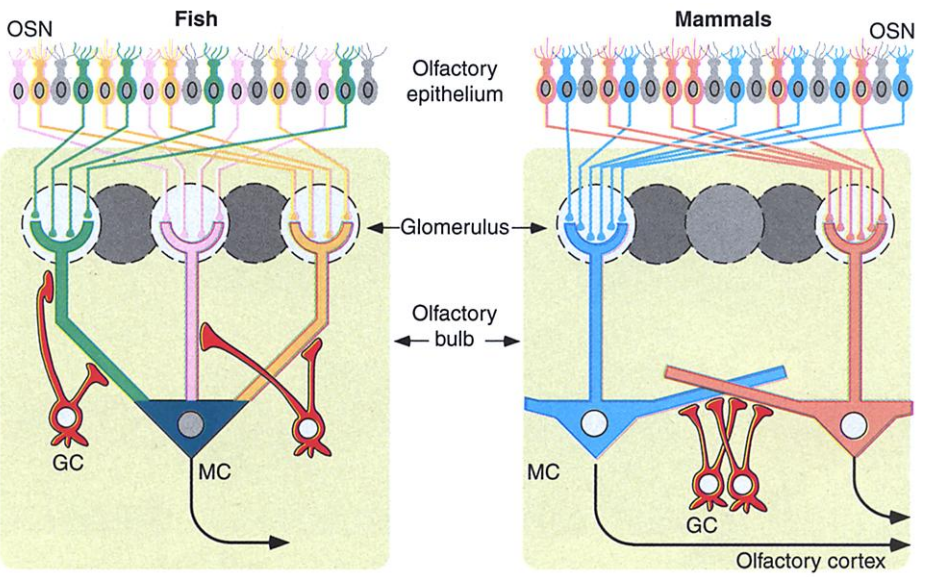
A sense of smell (olfaction) is an essential feature of most animal species, from insects and fish to mammals. An enormous number of odorant molecules are recognized by odorant receptors expressed on the surface of sensory neurons in the olfactory epithelium (*1*). Each neuron carries only one type of odorant receptor, and this receptor is activated by a range of odorants with similar structures. The axons of olfactory neurons send odor information encoded as electrical impulses to the olfactory bulb. Here, the axons form synapses with the dendrites of mitral cells, which are clustered together in spherical structures called glomeruli (see the figure). The mitral cells then convey the odor information to the olfactory cortex. Recent studies in mammals and insects have shown that individual glomeruli receive converging information from axons carrying signals from the same type of odorant receptor. Thus, the spatial arrangement of glomeruli on the surface of the olfactory bulb provides an odorant receptor map, showing regions where specific sets of odorant receptors are represented (*2, 3*). In zebrafish, for example, amino acid odorant molecules activate glomeruli in the lateral region of the olfactory bulb, whereas bile acid odorants activate glomeruli in the medial region (*4*).

There are, however, several striking differences between the fish and mammalian olfactory bulb—in fish, individual mitral cells project several dendrites onto multiple glomeruli, whereas in mammals, single mitral cells project a primary dendrite onto a single glomerulus. Thus, a single fish mitral cell receives sensory information from several different odorant receptors. But how does the multiglomerular mitral cell of fish read the odorant receptor map? Friedrich and Laurent (*5*) have set out to answer this question by recording from single mitral cells in the amino acid–sensitive region of the zebrafish olfactory bulb. On page 889 of this issue, they report that the response specificity of individual zebrafish mitral cells to odorants changes slowly over the course of 1 second. Introduction of a time component into the integration of dendritic signals enables the mitral cell to receive information from different groups of odorant receptors at different times.

The zebrafish is fast becoming one of the most useful model organisms for neuroscientists—olfactory researchers included. The zebrafish olfactory system is less complex than that of mammals with about 10-fold fewer odorant receptor genes (*1*) and glomeruli (*6*). The basic neuronal circuitry of the fish olfactory bulb is similar to that of other vertebrates (*7*). The principal difference is that fish mitral cells have several dendrites projecting onto multiple glomeruli, as opposed to mammalian mitral cells, which have a single primary dendrite projecting onto one glomerulus (multiglomeruli versus single-glomerulus mitral cells). This difference in the pattern of dendritic projections is extremely important when analyzing mitral cell responses to odorants, because direct integration of different odorant receptor information by a single mitral cell is only possible in the "multiglomeruli" system of fish. The temporal change in the odorant representations of zebrafish multiglomeruli mitral cells (*5*) differs from the response pattern of mammalian single-glomerulus mitral cells (*2, 8*). The odorant response specificity of each mammalian mitral cell strongly reflects that of the glomerulus into which it projects its single dendrite.

How do zebrafish mitral cells integrate the different incoming signals from multiple glomeruli? Of prime importance is the local neuronal circuitry in the olfactory bulb, which includes not only connections between olfactory axons and mitral cells in the glomeruli but also synapses between the dendrites of mitral cells and inhibitory interneurons called granule cells (see the figure). Mammalian granule cells form inhibitory synapses with the secondary dendrites of mitral cells (which do not project onto glomeruli) and mediate lateral inhibition between mitral cell neighbors (which sharpens odorant representation patterns) (*9*). In contrast, fish granule cells form inhibitory synapses on the shafts of the mitral



Zebrafish pick up the scent. Each olfactory sensory neuron (OSN) of the nasal epithelium expresses only one type of odorant receptor. Axons from sensory neurons expressing the same type of odorant receptor converge onto a few topographically fixed glomeruli in the olfactory bulb. Between fish (**left**) and mammals (**right**), there are two obvious differences in the neuronal connectivity pattern of the olfactory bulb. In fish, individual mitral cells (MC) project dendrites onto multiple glomeruli, whereas in mammals, individual mitral cells project a single primary dendrite onto a single glomerulus. The patterns of synaptic connections between the dendrites of mitral cells and those of granule cells (GC) also differ between fish and mammals. Fish granule cells form inhibitory synapses along the shafts of the mitral cell dendrites that project onto multiple glomeruli. In contrast, mammalian granule cells form inhibitory synapses along the mitral cell secondary dendrites that do not project onto glomeruli. These cells mediate lateral inhibition between neighboring mitral cells.

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cell dendrites that innervate the glomeruli. Fish granule cells could inhibit transfer of odorant information from the glomeruli to the mitral cells by shunting excitatory currents or by preventing spike conduction along the dendrites. If the sensory information arriving from individual dendrites is differentially controlled by granule cells, mitral cells would be able to receive information from select glomeruli. By altering the timing of granule cell-induced inhibition of individual dendrites, a mitral cell may be activated by different sets of glomerular inputs at different times. Thus, the representation of odorants by an ensemble of mitral cells would change with time, which is just what Friedrich and Laurent describe (*5*). This scenario is reminiscent of that in rabbit retinal ganglion cells that convey information about the directional selectivity of visual stimuli. Arrival of visual information at the dendrites of direction-selective ganglion cells depends on a balance between the excitatory inputs from bipolar cells, which allow signals to pass along the dendrites, and the inhibitory inputs from amacrine cells, which do not (*10*).

What is the advantage of the slow change in response specificity to odorants in zebrafish mitral cells? Working on their zebrafish brain explant with the nose attached, Friedrich and Laurent set up their experiments such that the fish's nose was stimulated over the course of 1 second by a continuous stream of odorants. Their analysis of odorant representations under these conditions led the authors to propose that the slow change in mitral cell responses might afford both a coarse classification of odorants during the initial response phase and a much finer discrimination later on.

Odorants in both water and air, however, typically form a plume that rapidly and continuously changes its shape; thus, an animal's nose encounters odorants intermittently. In their search for food or a mate, fish actively swim around and mammals keenly sniff the air to sample odorants. It is therefore possible that fish mitral cells with multiple glomeruli evolved to respond selectively to the changing patterns of certain odorants in water. Evidence from work by Christensen and Hildebrand (*11*) in the multiglomeruli projection neurons (equivalent to vertebrate mitral cells) of the antennal lobe of male sphinx moths suggests that this might be the case. Single projection neurons send dendrites to two glomeruli within a macroglomerular complex. Each member of the pair of glomeruli receives sensory information from olfactory neurons about one of the two key components of the female sphinx moth sex pheromone. Responses of projection neurons to short repetitive pulses of sex pheromones indicate that the two key components activate opposing synaptic inputs at the two different glomeruli. This enables the multiglomeruli projection neurons to replicate the duration and frequency of intermittent odorant pulses. Frequency coding by these neurons may be important as the male moths fly in a zig zag path, attempting to trace the intermittent plume of female sex pheromone.

Each type of neuron typically has its own characteristic branching pattern of dendrites and receives specific synaptic inputs only on selected parts of the dendritic arbor. How individual neurons integrate information from synapses spread across their broad dendritic tree remains unclear. In the multiglomeruli mitral cells of fish, each dendrite connects with a defined glomerulus, which receives incoming signals from only one type of odorant receptor (see the figure). Thus, fish mitral cells may strategically arrange different odorant receptor inputs on different dendrites, and may introduce a time component to enable switching of the flow of incoming signals from one dendrite to another. The multi-glomeruli mitral cells of zebrafish are an excellent model system with which to explore how individual neurons integrate a multitude of incoming sensory information.

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PERSPECTIVES: COSMOLOGY

In Support of Inflation

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What created the initial inhomogeneities in the universe that resulted in galaxies, clusters of galaxies, and other large-scale structures? This problem continues to puzzle cosmologists. But whatever the mechanism, it must have left its signature in the cosmic microwave background (CMB) radiation (*1*). The CMB is a relic of the Big Bang, a cold bath of light just a few degrees above absolute zero that pervades the entire universe. Released when matter began to become structured, the CMB is our earliest "snapshot" of the universe. Variations (or anisotropies) in its effective temperature tell us about the size and strength of the initial seeds in the primordial plasma, those clouds of gas that clumped together under gravitational attraction and led to the birth of galaxies. Recent CMB experiments suggest that these fundamental seeds could have resulted from tiny quantum fluctuations generated in the early universe during a period of rapid (faster than light) expansion called inflation.

Early on, when the universe was small and very hot, the free electron density was so high that photons could not propagate freely without being scattered by electrons. Ionized matter, electrons, and radiation formed a single fluid, in which the inertia is provided by the baryons (particles that have mass) whereas the photons exert a net outward pressure that halts gravitational collapse. An important property of this fluid was that it supported sound waves. The gravitational clumping of the effective mass was resisted by the restoring radiation pressure, resulting in gravity-driven acoustic oscillations in both fluid density and local velocity.

As the universe expanded and ambient temperatures decreased, high-energy collisions became less and less frequent. The now relatively low-energy photons could not destroy the increasing number of neutral particles (mostly hydrogen) that began to combine. Cosmologists refer to this period as recombination. Soon afterward, the CMB stopped interacting with electrons, making what is called its last scattering upon matter. This is a remarkable event in the history of the universe, because it is the very moment when it passed from being opaque to being transparent to electromagnetic radiation.

Features in the radiation pattern at this time depend on the maximum distance a sound wave could have traveled since the Big Bang. This distance is called the sound horizon. At the time of recombination, the sound horizon was much smaller than it is today (see the bottom figure, next page). To relate the distance between

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