New Whiffs About Chemesthesis. Focus on “TRPM5-Expressing Solitary Chemosensory Cells Respond to Odorous Irritants”

Anna Menini and Simone Pifferi
Sector of Neurobiology, International School for Advanced Studies, and Italian Institute of Technology, Trieste, Italy

In the recent article by Lin and collaborators (2008), they show that solitary chemosensory cells dispersed in the respiratory epithelium of the mouse nasal cavity could comprise a new transduction system for some noxious stimuli. Chemical sensitivity in the nasal cavity is not limited to smelling odors but extends to reacting to irritating stimuli eliciting sensations such as irritation, tickling, burning, stinging, warming, and cooling. These latter sensations are not mediated by the olfactory nerve but by the trigeminal nerve that also innervates the nasal cavity. It has been assumed for a long time that chemical irritants directly act on free nerve endings (for review, see Bryant and Silver 2000; Doty et al. 1978). Sensations arising from chemical irritants are components of the “common chemical sense” (Parker 1912), later named chemesthesis (Green et al. 1990). While the most effective chemesthetic stimuli, lipophilic molecules, diffuse through cell membranes to reach sensory nerve fibers directly, it is less clear how hydrophilic compounds stimulate free nerve endings buried within the epithelial layer. This puzzle has now been solved by the finding that solitary chemosensory cells within the nasal epithelium directly respond to high concentrations of odorous molecules, including hydrophilic ones (Lin et al. 2008).

Solitary chemosensory cells, located in the anterior respiratory epithelium of the nasal cavity of rodents, express T2R “bitter-taste” receptors and α-gustducin, a G protein α subunit expressed in taste receptor cells (Finger et al. 2003). Moreover, Kaske et al. (2007) have shown that in the mouse nasal epithelia, there are solitary chemosensory cells expressing TRPM5, a calcium-activated nonselective cation channel belonging to the large family of transient receptor potential channels that plays a fundamental role in taste transduction (Perez et al. 2002; Zhang et al. 2003). Lin et al. (2008) confirmed the presence of solitary chemosensory cells expressing TRPM5 using transgenic mice in which the expression of green fluorescent protein is under the control of TRPM5 promoter. They found a population of ~11,200 solitary chemosensory cells expressing TRPM5 in the respiratory epithelium especially concentrated near the entry of the nasal cavity. These cells are elongated with an apical process that reaches the luminal surface. They lack any detectable axonal process and have morphological features similar to those of α-gustducin-positive solitary chemosensory cells. However, Lin et al. (2008) showed that some, but not all, TRPM5-expressing cells also express α-gustducin, indicating that the nasal respiratory epithelium contains solitary cells with different sensory properties. Further the authors found that several TRPM5-expressing cells express components of the PLC pathway, such as PLCβ2 and γ13, that in taste receptor cells are involved in the activation of TRPM5 (Liman 2007). However, some cells did not express PLCβ2 and γ13, further evidence for multiple mechanisms of transduction.

But do these solitary cells connect to the nervous system? The authors confirmed and extended previous ultrastructural studies by Finger et al. (2003) showing that peptidergic nerve fibers, stained with PGP9.5 or with substance P, closely appose solitary chemosensory cells, running along the length of the cells or wrapping their basal region. This organization would allow sensory signal transmission to trigeminal fibers, perhaps through synaptic transmission. Indeed Lin et al. (2008) found immunoreactivity for synaptobrevin-2 in the same cells indicating that they may transmit sensory information onto nerve fibers through synaptic transmission.

What about the functional role of the TRPM5-expressing solitary chemosensory cells? Two types of approaches were used by Lin et al. (2008): electrophysiological recordings from areas containing these cells and Ca2+ imaging recordings from dissociated cells. In the first set of functional experiments, the authors measured local field potentials (event-related potentials) (Hummel 2000; Rombaux et al. 2006) on stimulation of various odors such as citral, lilial, butanone, or menthone and obtained significant responses only with high concentrations (1–5 mM), in agreement with the well-known low sensitivity to odors of the trigeminal system (Bryant and Silver 2000; Doty et al. 1978). Control experiments indicated that the responses were due to the activation of the trigeminal system, but both free nerve endings and the cells under study could contribute to the measured local field potentials. Do TRPM5-expressing solitary chemosensory cells respond to irritants? To answer this question, the authors performed Ca2+ imaging experiments on dissociated cells and measured an increase in intracellular Ca2+ concentration in response to chemical stimuli at high concentrations, thus providing the first direct demonstration that solitary chemosensory cells respond to odorous irritants. It is also of interest to note that most cells responded to multiple, but not all, stimuli tested, suggesting that they may be selectively tuned, albeit broadly so.

These new findings indicate the existence of heterogenous populations of specialized solitary chemosensory cells in the nasal respiratory epithelium that may bind potentially irritant or harmful chemicals and, through activation of transduction cascades, activate the trigeminal system. Future studies will have to establish the physiological role that solitary chemosensory cells play in nasal chemesthesis and identify the subpopulation profile of these cells, their signal transduction cascades, adaptation properties, and their interplay with direct activation of free nerve endings by lipophilic compounds.
REFERENCES


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