Commentary

New Kid on the Block: A Role for the Na/Ca Exchanger in Odor Transduction

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Odors seem the most subtle of sensory stimuli, yet our ability to detect them is robust, and their capacity to influence our actions is profound. Although scientists have studied olfaction for >2,000 yr, advances in understanding the cell physiology of odor detection have occurred especially rapidly in the past decade since the application of the patch clamp technique (Anderson and Ache, 1985; Trotier, 1986). Important roles for G protein–coupled receptors, intracellular messengers, and certain ion channels in odor transduction were demonstrated (for review see Schild and Restrepo, 1998), and it seemed that the odor response might well be regulated in its entirety by these components or through modulation of them. Now, Reisert and Matthews (1998) present evidence that a Na/Ca exchanger appears to control the decline of the sensory transduction current in at least some frog olfactory receptor neurons. This observation extends the list of players that have been implicated in odor transduction and introduces a novel and additional means for cells to manage the odor response.

At the cellular level, odors are detected by olfactory receptor neurons, a specialized kind of bipolar neuron that is exposed at one end on the surface of the nasal epithelium and connected at the other end to the central nervous system by synapses in the olfactory bulb. When the neurons detect odors in the nasal airway, they respond with quick but transient changes in excitability, resulting in a pattern of action potentials, encoding information about the odor and sending it directly to the brain.

At the molecular level, odor responses are produced by G protein–coupled receptors that modulate the levels of intracellular second messengers (Shepherd, 1994). Several such pathways have been implicated in odor transduction, but by far the best studied is one that uses cyclic AMP. The cyclic AMP pathway is activated when odor molecules bind to specific G protein–coupled receptors on the apical cilia of olfactory receptor neurons and, through the action of a G protein, possibly G_{OLF}, activate type III adenylyl cyclase, thus elevating intracellular cAMP. Cyclic AMP can bind to cyclic nucleotide–gated (CNG) cation channels causing them to open; this channel, which occurs at high density in the ciliary membrane of many olfactory receptor neurons, is primarily permeable to Ca^{2+} under physiological conditions. Calcium influx through the channel activates a secondary current carried by Cl^- ions through Ca-gated Cl^- channels; it is this secondary current that produces most of the receptor potential. Together, these primary and secondary conductances depolarize the olfactory neuron. In a high percentage of frog olfactory receptor neurons, cineole, a fragrant extract from eucalyptus, reliably activates the cyclic AMP pathway; this was the experimental preparation used by Reisert and Matthews (1998) to study the mechanism of termination of the transduction current.

The cyclic AMP–associated transduction current is turned on with a latency of several hundred milliseconds after exposure to odor, and turned off over the course of a second or so, typically outlasting brief odor pulses. The long activation latency reflects the time needed for the second messenger pathway to be activated, and each step along the activation pathway represents a potential regulatory site for endogenous control of the response. Processes such as modulation by intracellular Ca/calmodulin of the affinity of the CNG cation channel for cyclic AMP, and modulation by cyclic GMP of the kinetics of the CNG channel, regulate the odor response by acting on the activation pathway. In fact, the transduction current shows adaptation, rundown, hormonal modulation, and possibly other forms of plasticity, attesting to the importance of regulation on neuronal excitability. Into the light of this emphasis on the activation pathway step Reisert and Matthews (1998), who look at termination of the transduction current. They show that termination of the current mirrors a decline in intracellular Ca^{2+} and conclude that this decline is controlled by a Na/Ca exchange mechanism. This introduces a new player in the olfactory arena and, possibly more importantly, a new mechanism whose regulation may explain additional forms of modulation of odor transduction.

Like in other sensory systems, the mechanisms underlying olfactory transduction are becoming increasingly complex. Presumably, it is this complexity with its inherent feedback and control pathways that helps insure the robustness of the olfactory response.

J. GEN. PHYSIOL. © The Rockefeller University Press • 0022-1295/98/11/527/2 $2.00
Volume 112 November 1998 527–528
http://www.jgp.org

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