OLFACTION

Autonomic Modulation of Olfactory Signaling

Randy A. Hall*

The olfactory epithelium is extensively innervated by sympathetic nerve endings, which release norepinephrine, and parasympathetic nerve endings, which release acetylcholine. Because olfactory sensory neurons have adrenergic and muscarinic receptors in addition to odorant receptors, autonomic stimulation can modulate the responses of olfactory sensory neurons to odorants. Recent studies have shed light on the molecular mechanisms that underlie crosstalk between muscarinic and odorant receptor signaling. The emerging view is that the stimulation of odorant receptor signaling by odorants, which is the earliest step in olfaction, can be substantially regulated by the autonomic nervous system.

How sophisticated is your nose? The nose was once believed to be nothing more than a simple sensor that delivered olfactory information, such as the smell of a freshly cut lawn or a plate of warm chocolate-chip cookies, directly to the brain in an unprocessed format. However, this perspective on olfactory signaling has been evolving over the past few decades, because it has become clear that a substantial amount of information processing occurs well before olfactory information ever gets to the brain. A study by Li and Matsunami (*1*) continues this shift in thinking by providing new insights into how odorant receptor signaling is modulated by the autonomic nervous system. These findings suggest that your nose is sophisticated enough to differentially interpret odor information depending on such factors as arousal level and the interplay between the sympathetic and parasympathetic nervous systems.

Olfaction begins in the olfactory epithelium, which consists mainly of olfactory sensory neurons (OSNs) and supporting sustentacular cells. Odorants float into the nasal cavity and bind to specific odorant receptors (ORs) found in the OSN cilia. The ORs constitute a family of several hundred heterotrimeric guanine nucleotide–binding protein (G protein)–coupled receptors (GPCRs), each with distinct preferences for binding to odorants. In addition to ORs, OSNs also have more than 30 other types of GPCRs, including receptors activated by norepinephrine (also known as noradrenaline) and acetylcholine (*1*–*5*). The olfactory epithelium is innervated by autonomic nerves, including sympathetic nerve endings, which release norepinephrine (*6*–*9*), and parasympathetic nerve endings, which release acetylcholine (Fig. 1) (*6*, *7*, *9*). Thus, autonomic neurotransmitters are secreted in the vicinity of OSNs, which have the receptors to bind to them.

The sympathetic nervous system mediates the "fight or flight" response and becomes activated during periods of stress. Conversely, the parasympathetic nervous system mediates the "rest and digest" response and is active during feeding and at other times when stress levels are low. Autonomic regulation of sensory signaling in the visual system has been intensively studied for more than 100 years, and the mechanisms of visual regulation by norepinephrine and acetylcholine have been described in exquisite detail (*10*). Autonomic regulation of vision is important because your visual needs are very different when you are fleeing a predator than when you are calmly preparing food for a meal. However, in contrast to the attention that has been lavished on autonomic regulation of vision, much less is known about the regulation of the other senses by the sympathetic and parasympathetic systems.

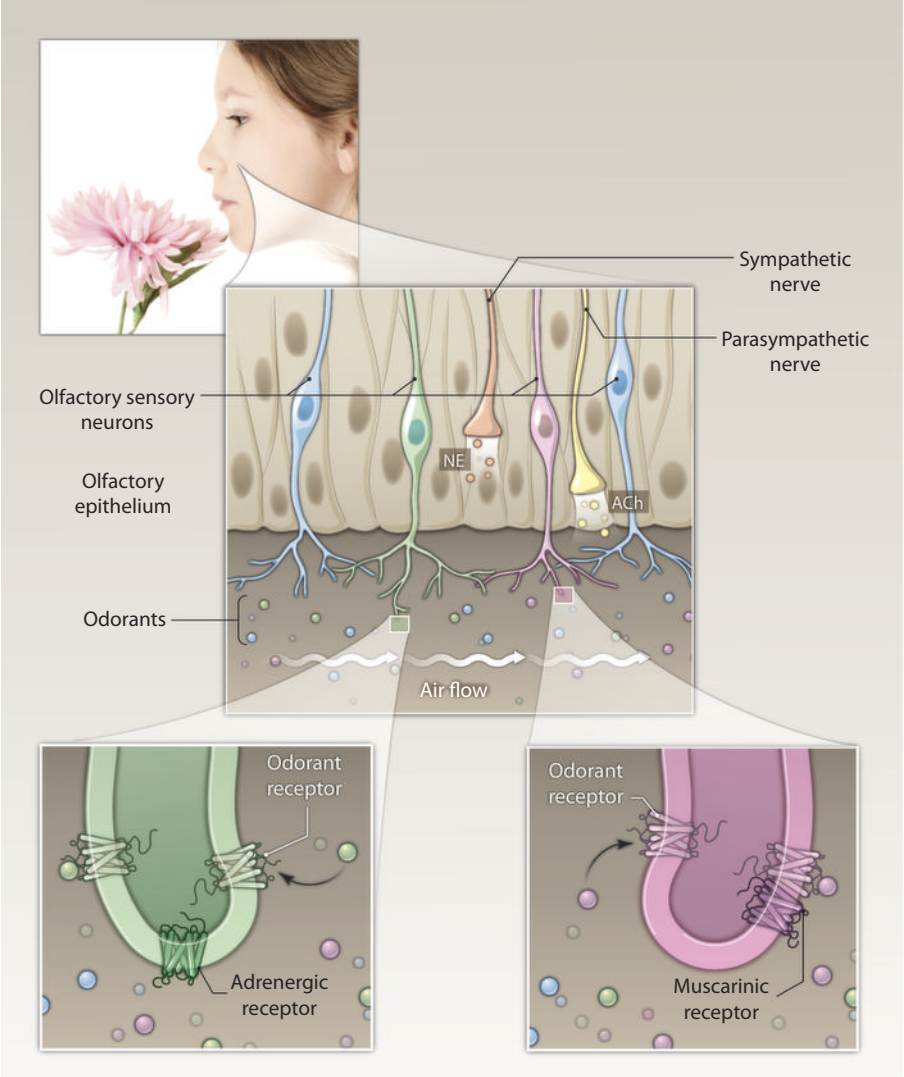
Autonomic neurotransmitters in the olfactory epithelium act on sustentacular cells (*11*) and blood vessels (*12*) to modulate olfaction indirectly, but they can also exert direct effects on OSNs. For example, norepinephrine enhances the maximal amplitude of electro-olfactogram responses induced by specific odorants (*13*). Furthermore, the stimulation of adrenergic receptors enhances odorant contrast by raising the threshold for spike initiation in OSNs while simultaneously amplifying responses to strong stimuli (*14*, *15*). The molecular mechanisms that underlie sympathetic regulation of OSNs involve phosphorylation-dependent changes in the activities of several different ion channels, which result in a shift in the response profiles of OSNs (*14*).

Similar to norepinephrine, acetylcholine can also potentiate OSN activity (*16*), and antagonists of muscarinic acetylcholine receptors reduce the responses of OSNs to odorants (*1*, *17*). Systemic application of cholinergic agonists enhances olfactory discrimination of a broad array of odorants and promotes olfactory learning (*18*). Some of these cholinergic effects on olfactory discrimination are on neural circuits in the olfactory bulb and other brain regions, but cholinergic modulation of olfaction starts with direct effects on OSNs (*1*, *2*, *16*). The mechanisms underlying these direct cholinergic actions on OSNs are the focus of the recent work by Li and Matsunami, who showed that the M3 muscarinic acetylcholine receptor (M3-R) was abundant in OSN cilia (*1*). Interestingly, the M3-R formed complexes with ORs to promote odorant-induced responses. Furthermore, odorant responses mediated by M3-R-OR complexes were enhanced by agonists and blocked by antagonists of muscarinic receptors. These data suggest that acetylcholine can modulate the very first step in olfaction, the activation of ORs by odorants.

Interactions between different GPCRs have been intensively studied over the past decade as a mechanism that underlies crosstalk between intersecting signaling systems (*19*–*21*). ORs are capable of interactions with certain types of GPCRs (*22*–*26*), although the physiological importance of these associations for OR function in native OSNs has been unclear. The work by Li and Matsunami clarifies this situation by demonstrating both the colocalization and functional importance of complexes of M3-Rs and ORs in OSNs (*1*). The association of M3-R with ORs both potentiated odorant-induced responses and switched the signaling pathway used by at least one OR subtype from the traditional pathway involving stimulation of $G\alpha_{olf}$ and the generation of cyclic adenosine monophosphate (cAMP) to a pathway involving the stimulation of $G\alpha_{q}$ and the mobilization of intracellular calcium ions (Ca^{2+}), a pathway to which the M3-R normally couples. Similar observations of interactions of ORs with other GPCRs that switch the G protein–coupling preferences of the ORs have been described for OR interactions with purinergic receptors (*24*) and may contribute to the diversity

Department of Pharmacology, Emory University School of Medicine, Atlanta, GA 30322, USA.

***E-mail, rhall@pharm.emory.edu**



CREDIT: Y. HAMMOND/*SCIENCE SIGNALING*

Fig. 1. Autonomic modulation of the earliest steps of olfactory signaling. Norepinephrine (NE) released by sympathetic nerves and acetylcholine (ACh) released by parasympathetic nerves both can modulate the responses of olfactory sensory neurons to odorants. Stimulation of adrenergic receptors, in either the cilia (as shown here) or cell body (not shown), results in downstream changes in ion channel activity and olfactory sensory neuron output, whereas muscarinic acetylcholine receptors can form complexes with odorant receptors in the olfactory cilia to directly control odorant receptor activity.

of G protein–mediated pathways that are stimulated by different odorants (*27*–*29*).

What do these findings mean for autonomic modulation of olfactory signaling? Specifically, because sympathetic and parasympathetic systems tend to oppose each other in most organs, why do both adrenergic and cholinergic modulation of OSNs seem to enhance responses to odorants? One possibility is that adrenergic and cholinergic modulation may enhance olfaction in different ways. If adrenergic stimulation enhances odorant contrast, filtering out weak responses and amplifying strong ones (*14*), this enhanced focus on the strongest and most salient olfactory cues might be beneficial in times of great stress, when focus is required. In contrast, if cholinergic modulation of olfaction more broadly increases responses to many odorants (*1*), this might correlate with an enhanced appreciation for the richness and complexity of olfactory cues in a way that may be beneficial during feeding. Future work in this area will seek to shed light on the physiological importance of autonomic modulation of olfaction in vivo and also strive to further clarify the molecular mechanisms that underlie the effects of norepinephrine, acetylcholine, and other neurotransmitters on OSN signaling. What is clear, though, is that a substantial amount of information processing occurs during the earliest steps of olfaction, which means that your nose may be a lot more sophisticated than you might think.

References

1. Y. R. Li, H. Matsunami, Activation state of the M3 muscarinic acetylcholine receptor modulates mammalian odorant receptor signaling. *Sci. Signal.* **4**, ra1 (2011).
2. B. Hedlund, G. M. Shepherd, Biochemical studies on muscarinic receptors in the salamander olfactory epithelium. *FEBS Lett.* **162**, 428–431 (1983).
3. C. C. Hegg, D. Greenwood, W. Huang, P. Han, M. T. Lucero, Activation of purinergic receptor subtypes modulates odor sensitivity. *J. Neurosci.* **23**, 8291–8301 (2003).
4. D. Czesnik, D. Schild, J. Kuduz, I. Manzini, Cannabinoid action in the olfactory epithelium. *Proc. Natl. Acad. Sci. U.S.A.* **104**, 2967–2972 (2007).
5. N. Sammeta, T. T. Yu, S. C. Bose, T. S. McClintock, Mouse olfactory sensory neurons express 10,000 genes. *J. Comp. Neurol.* **502**, 1138–1156 (2007).
6. J. J. Grote, W. Juijpers, P. L. Huygen, Selective denervation of the autonomic nerve supply of the nasal mucosa. *Acta Otolaryngol.* **79**, 124–132 (1975).
7. B. S. Zielinski, M. L. Getchell, R. L. Wenokur, T. V. Getchell, Ultrastructural localization and identification of adrenergic and cholinergic nerve terminals in the olfactory mucosa. *Anat. Rec.* **225**, 232–245 (1989).
8. Y. Chen, T. V. Getchell, D. L. Sparks, M. L. Getchell, Patterns of adrenergic and peptidergic innervation in human olfactory mucosa: Age-related trends. *J. Comp. Neurol.* **334**, 104–116 (1993).
9. J. N. Baraniuk, S. J. Merck, Neuroregulation of human nasal mucosa. *Ann. N.Y. Acad. Sci.* **1170**, 604–609 (2009).
10. B. Gilmartin, A review of the role of sympathetic innervation of the ciliary muscle in ocular accommodation. *Ophthalmic Physiol. Opt.* **6**, 23–37 (1986).
11. M. L. Getchell, T. V. Getchell, Fine structural aspects of secretion and extrinsic innervation in the olfactory mucosa. *Microsc. Res. Tech.* **23**, 111–127 (1992).
12. D. A. Johnson, J. G. Hricik, The pharmacology of alpha-adrenergic decongestants. *Pharmacotherapy* **13**, 110S–115S; discussion, 143S–146S (1993).
13. H. Aréchiga, C. Alcocer-Cuarón, Adrenergic effects on electro-olfactogram. *Exp. Med. Surg.* **27**, 384–394 (1969).
14. F. Kawai, T. Kurahashi, A. Kaneko, Adrenaline enhances odorant contrast by modulating signal encoding in olfactory receptor cells. *Nat. Neurosci.* **2**, 133–138 (1999).
15. S. Firestein, A. Menini, The smell of adrenaline. *Nat. Neurosci.* **2**, 106–108 (1999).
16. J. F. Bouvet, J. C. Delaleu, A. Holley, The activity of olfactory receptor cells is affected by acetylcholine and substance P. *Neurosci. Res.* **5**, 214–223 (1988).
17. S. Firestein, G. M. Shepherd, Neurotransmitter antagonists block some odor responses in olfactory receptor neurons. *Neuroreport* **3**, 661–664 (1992).
18. D. A. Wilson, M. L. Fletcher, R. M. Sullivan, Acetylcholine and olfactory perceptual learning. *Learn. Mem.* **11**, 28–34 (2004).

19. S. Terrillon, M. Bouvier, Roles of G-protein-coupled receptor dimerization. *EMBO Rep.* **5**, 30–34 (2004).
20. S. C. Prinster, C. Hague, R. A. Hall, Heterodimerization of G protein-coupled receptors: Specificity and functional significance. *Pharmacol. Rev.* **57**, 289–298 (2005).
21. G. Milligan, G protein-coupled receptor heterodimerization: Contribution to pharmacology and function. *Br. J. Pharmacol.* **158**, 5–14 (2009).
22. C. Hague, M. A. Uberti, Z. Chen, C. F. Bush, S. V. Jones, K. J. Ressler, R. A. Hall, K. P. Minneman, Olfactory receptor surface expression is driven by association with the beta2-adrenergic receptor. *Proc. Natl. Acad. Sci. U.S.A.* **101**, 13672–13676 (2004).
23. C. Hague, R. A. Hall, K. P. Minneman, Olfactory receptor localization and function: An emerging role for GPCR heterodimerization. *Mol. Interv.* **4**, 321–322 (2004).
24. C. F. Bush, S. V. Jones, A. N. Lyle, K. P. Minneman, K. J. Ressler, R. A. Hall, Specificity of olfactory receptor interactions with other G protein-coupled receptors. *J. Biol. Chem.* **282**, 19042–19051 (2007).
25. C. F. Bush, R. A. Hall, Olfactory receptor trafficking to the plasma membrane. *Cell. Mol. Life Sci.* **65**, 2289–2295 (2008).
26. R. A. Hall, Olfactory receptor interactions with other receptors. *Ann. N.Y. Acad. Sci.* **1170**, 147–149 (2009).
27. G. V. Ronnett, H. Cho, L. D. Hester, S. F. Wood, S. H. Snyder, Odorants differentially enhance phosphoinositide turnover and adenylyl cyclase in olfactory receptor neuronal cultures. *J. Neurosci.* **13**, 1751–1758 (1993).
28. A. Kato, K. Touhara, Mammalian olfactory receptors: Pharmacology, G protein coupling and desensitization. *Cell. Mol. Life Sci.* **66**, 3743–3753 (2009).
29. K. Klasen, E. A. Corey, F. Kuck, C. H. Wetzel, H. Hatt, B. W. Ache, Odorant-stimulated phosphoinositide signaling in mammalian olfactory receptor neurons. *Cell. Signal.* **22**, 150–157 (2010).

10.1126/scisignal.2001672

Citation: R. A. Hall, Autonomic modulation of olfactory signaling. *Sci. Signal.* **4**, pe1 (2011).