

Symposium Overview

Nasal Trigeminal Function: Qualitative, Quantitative, and Temporal Effects

**Session Cochairs: Dennis Shusterman^a
and Thomas Hummel^b**

^a*University of California, San Francisco, California, USA*

^b*University of Dresden, Dresden, Germany*

The nasal cavity is innervated by two cranial nerves: the olfactory (Cr. N. I) and the trigeminal (Cr. N. V). These structures together convey the sense of smell (I) and nasal pungency (V). These percepts are normally integrated in everyday life, as is implicit in references to, for example, “pungent odors.” Nasal pungency (often referred to as “irritation”) is an essential component of our response to foods, selected medications and cosmetics, and many air pollutants. Despite its obvious functional importance, however, nasal trigeminal function has commanded relatively modest scientific attention and resources, particularly when compared to its companion senses of smell and taste.¹

The distinction between olfaction and nasal trigeminal chemoreception dates at least back to 1912, when Parker coined the term “common chemical sense” to describe the nonolfactory, nontaste chemical responsiveness of mucous membranes in vertebrates.² Despite confusion regarding the word “common” (did it refer to the sensory apparatus or the nature of the stimuli?), the term continued to be used without serious debate at least until the 1960s. In 1964, Keele and Armstrong proposed the term “chemalgia,” highlighting the nociceptive nature of the sense.³ However, in 1990 Green

et al. suggested instead “chemesthesis,” the rationale being that the trigeminal nerve conveys both painful and nonpainful sensations.⁴

Neuroanatomically, the trigeminal nerve (with its three branches: ophthalmic, maxillary, and mandibular) supplies the mucous membranes of the eyes, nose, oral cavity, and nasopharynx with *general somatic afferent* fibers. Thus neurobiologically, perception of nonolfactory, nontaste chemical stimulation could be termed “chemo-somatosensation,” a term proposed by Kobal and [C.] Hummel in 1988.⁵ From a toxicologist’s perspective, the constellation of eye, nose, and throat irritation has been termed “sensory irritation.”⁶ More broadly, however, identical transduction phenomena can occur in cutaneous nerves and therefore are not limited to mucous membranes.⁷ Here we will confine our attention to the nasal cavity and will use the neutral terminology “trigeminal chemoreception.”

A corollary to naming a sensory modality is naming the corresponding sensory apparatus. Nerve fibers responsive to nonolfactory, nontaste chemical stimuli generally consist of either unmyelinated (C) or small-diameter myelinated (A δ) fibers, initially thought to terminate in the skin or mucous membranes solely as “free nerve endings.” Bessou and Perl, in studying the responsiveness of high-threshold cutaneous C fibers responsive to mechanical, thermal, and chemical stimuli, in 1969 termed these “polymodal nociceptors,” implying both the *pain modality* and a *lack of specificity*.⁸

Address for correspondence: Dennis Shusterman, MD, MPH, UCSF Box 0843, San Francisco, CA 94143-0843. Voice: 510-620-5714; fax: 510-620-5743. dshusterman@sfghoem.ucsf.edu

Discovery of the *axon reflex* (release of vasoactive neuropeptides from afferent cutaneous or mucosal nerves) led to a further distinction between fibers that do contain substance P and those that do not (a distinction that often, but not invariably, tracks with fiber type).^{9–11} Differentiation of chemical responsiveness among different fiber populations was demonstrated electrophysiologically by Sekizawa and Tsubone in 1994, establishing a potential neural substrate for perceptual specificity within the nasal trigeminal system.¹² Most recently, the discovery that trigeminal afferents may synapse with specialized *solitary chemoreceptor cells* embedded in the oral or nasal mucosa—and the fact that solitary chemoreceptor cells can respond to vapor-phase irritant chemicals—raises the prospect of a paradigm shift of major proportions.^{13–15}

Nasal chemosensory diversity has clearly reached its evolutionary pinnacle in the olfactory system. Nevertheless, recent psychophysical, electrophysiologic, and molecular biologic studies highlight the potential for qualitative “texture” in nasal trigeminal function as well. The presentations at the International Symposium on Olfaction and Taste (ISOT) 2008 session Nasal Trigeminal Function: Qualitative, Quantitative, and Temporal Effects explored functional specialization within the nasal trigeminal system, as well as the potential for perceptual specificity. These review progress from the micro to the macro, and from the periphery to the center of the nervous system, culminating in psychophysics. Together they provide a fresh look at the system in light of recent imaginative research.

Representing the perspective of molecular neurobiology is Dr. Diana Bautista, a colleague of Dr. David Julius at the University of California, San Francisco. The Julius lab has been responsible for an explosion of information regarding nociceptive ion channels, beginning in 1997 with the cloning of the capsaicin (TRPV1) receptor. Moving to ensemble and single-fiber recording, Dr. Wayne Silver of Wake Forest University reviews peripheral

electrophysiologic studies in experimental animals documenting neural responsiveness to airborne irritants. At the central level, Dr. Thomas Hummel reviews electrophysiologic and functional central nervous system imaging studies. Finally, Drs. Paul Wise (Monell Chemical Senses Center) and Dennis Shusterman (University of California, San Francisco) review human psychophysical studies documenting temporal and qualitative trigeminal effects, respectively.

We hope that this series of reviews will help highlight research results, promote collaboration among scientists using diverse (but complementary) study tools, and help invigorate an area of research that deserves increased attention in the chemical senses.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Cain, W.S. 1976. Olfaction and the common chemical sense: some psychophysical contrasts. *Sens. Processes* **1**: 57–67.
2. Parker, G.H. 1912. The relations of smell, taste, and the common chemical sense in vertebrates. *J. Acad. Sci. Phila.* Ser 2 **15**: 221–234.
3. Keele, C.A. & D. Armstrong. 1964. Substances producing pain and itch. Monographs of the Physiological Society, No. 12. Arnold. London.
4. Green, B.G., J.R. Mason & M.R. Kare. 1990. Preface. In *Chemical Senses, Volume 2: Irritation*. B.G. Green, J.R. Mason & M.R. Kare, Eds.: v–vii. Marcel Dekker. New York.
5. Kobal, G. & C. Hummel. 1988. Cerebral chemosensory evoked potentials elicited by chemical stimulation of the human olfactory and respiratory nasal mucosa. *Electroencephalogr. Clin. Neurophysiol.* **71**: 241–250.
6. Alarie, Y. 1973. Sensory irritation by airborne chemicals. *CRC Crit. Rev. Toxicol.* **2**: 299–363.
7. Keele, C.A. 1962. The common chemical sense and its receptors. *Arch. Int. Pharmacodyn. Ther.* **139**: 547–557.
8. Bessou, P. & E.R. Perl. 1969. Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. *J. Neurophysiol.* **32**: 1025–1043.

9. Stjärne P, L. Lundblad, A. Anggård, *et al.* 1989. Tachykinins and calcitonin gene-related peptide: co-existence in sensory nerves of the nasal mucosa and effects on blood flow. *Cell Tissue Res.* **256**: 439–446.
10. Bryant, B. & W.L. Silver. 2000. Chemesthesis: the common chemical sense. In *The Neurobiology of Taste and Smell*. T.E. Finger, W.L. Silver & D. Restrepo, Eds.: 73–100. John Wiley & Sons. New York.
11. Taylor-Clark, T.E., M. Kloosari, *et al.* 2005. Nasal sensory nerve populations responding to histamine and capsaicin. *J. Allergy Clin. Immunol.* **116**: 1282–1288.
12. Sekizawa, S.I. & H. Tsubone. 1994. Nasal receptors responding to noxious chemical irritants. *Respir. Physiol.* **96**: 37–48.
13. Finger, T.E., B. Bottger, A. Hansen, *et al.* 2003. Solitary chemoreceptor cells in the nasal cavity serve as sentinels of respiration. *Proc. Natl. Acad. Sci. USA* **100**: 8981–8986.
14. Lin, W., T. Ogura, R.F. Margolskee, *et al.* 2008. TRPM5-expressing solitary chemosensory cells respond to odorous irritants. *J. Neurophysiol.* **99**: 1451–1460.
15. Gulbransen, B.D., T.R. Clapp, T.E. Finger & S.C. Kinnamon. 2008. Nasal solitary chemoreceptor cell responses to bitter and trigeminal stimulants in vitro. *J. Neurophysiol.* **99**: 2929–2937.