Qualitative Effects in Nasal Trigeminal Chemoreception

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Olfaction and nasal trigeminal chemoreception together convey an impression of the physical and chemical qualities of inspired air. "Nasal pungency" refers to the nasal trigeminal impact of inhaled air pollutants as well as spicy foods and selected medicaments. Such diverse sensations as cooling, numbness, tingling, itching, burning, and stinging are all conveyed by the trigeminal system yet are successfully differentiated in psychophysical testing, with or without concomitant olfactory information. Here we briefly review the neurobiological and psychophysical evidence for qualitative specificity in the nasal trigeminal system.

Key words: **trigeminal nerve; nasal irritation; qualitative encoding; sensory transduction**

In 1988 a series of meetings was held at Monell Chemical Senses Center to commemorate the 20th anniversary of the founding of that institution. One of these was entitled "The International Symposium on Chemical Irritation in the Nose and Mouth," and its proceedings were published in 1990 as *Chemical Senses, Volume 2: Irritation*, edited by Barry Green and others. In their introduction the editors proposed the term "chemesthesis" to replace "common chemical sense," further pointing out the watershed significance of the meeting as being the first devoted exclusively to the topic of oral and nasal irritation.[1] Despite its somewhat more modest scope, the 2008 symposium "Nasal Trigeminal Function: Qualitative, Quantitative and Temporal Effects," held within the International Symposium on Olfaction and Taste, provided an opportunity to take stock of the intervening 20 years' progress in the area.

Since 1988 much has transpired in our understanding of the chemical senses. Perhaps most dramatically, olfactory receptor proteins were sequenced, their intracellular signaling mechanism elucidated, olfactory circuits traced, and the anatomical foundations of qualitative encoding within the olfactory bulb explicated. So revolutionary was this series of developments that it resulted in the awarding of the Nobel Prize for Medicine to two sensory neurobiologists.

What corresponding progress has been made in the field of trigeminal chemoreception during the same period? As the preceding reviews document, we have seen a dramatic expansion of knowledge pertaining to nociceptive ion channels, *in vitro* imaging of trigeminal ganglion cells (and their chemical responsiveness), behavioral evaluation of knockout mice with deficient nociceptors, peripheral and central electrophysiology, functional imaging of the central nervous system, and temporal dynamics in psychophysics. That said, how challenging have these new data been to the prevailing paradigm?

As a starting point, we should take stock of the state of knowledge that prevailed 20 years ago. "Polymodal nociceptors" (chiefly but not exclusively unmyelinated C-fibers) had relatively recently been shown to include

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subpopulations containing vasoactive neuropeptides, and speculation was active regarding the potential role of the peripheral ("axon") reflex in modulating the function of both the respiratory and olfactory epithelium of the nose.[2] However, at that time there were no data challenging the premise that peripheral chemosensory transduction within the trigeminal nerve occurred exclusively at "free nerve endings."[2,3] More specifically, documentation of solitary chemoreceptor cells in the nasal mucosa (responsive to both bitter tastants and irritant chemicals) was still a decade and a half away.[4]

In peripheral electrophysiology, ensemble recordings from the ethmoid nerve of rats showed concentration–response relationships, concentration-dependent temporal dynamics, and structural dependency when comparing responses to various vapor-phase chemicals.[3] However, the fact that different fiber and ganglion cell populations might respond to different spectra of chemicals had not yet been documented using either single-fiber recordings or calcium imaging studies.[5–7]

Although the existence of receptors for noxious chemicals ("nociceptive ion channels") had been postulated, only the nicotinic acetylcholine receptor had been characterized at a molecular level (isoforms being identified the same year as the conference).[8] Since that time, the vanilloid receptor (TRPV1), purinergic receptors responsive to by-products of tissue damage (e.g., P2X), acid-sensitive ion channels (ASIC/DRASIC), and TRP channels responsive to menthol (TRPM8) or isothiocyanate (TRPA1) have been sequenced, studied electrophysiologically in transfected cells, and in many cases examined behaviorally in knockout mice.[9–13] (Of the above, TRPA1 appears to hold promise as responding to the widest range of chemicals of environmental concern.[14])

At the time of the 1988 conference, predominant opinion held that most nonreactive volatile organic compounds (VOCs), which typically have relatively high trigeminal detection thresholds, most likely produced sensory irritation via nonspecific perturbation of cell membranes.[15] As late as 1998 related discussions of physico–chemical models referred only to "the receptor area."[16] As reviewed below, both animal and human studies now suggest that receptors, albeit broadly tuned, may directly contribute to the perception of VOC-induced irritancy. Despite these early indications, it is fair to say that neither the detailed pharmacokinetics of a putative VOC receptor nor its molecular identity has been described to date. Further, the ability of selected VOCs (e.g., ethanol) to stimulate known receptors (e.g., TRPV1) may further complicate our understanding of this area.[17]

Although nasal trigeminal function had been credited with ". . .[a] pervasive influence in the perception of what we loosely call odor magnitude and odor quality" (p. 57), qualitative encoding in nasal trigeminal psychophysics was still largely unexplored.[18] As reviewed below, human experimental data now suggest that qualitative encoding within the nasal trigeminal system may be sufficiently robust, on its own, to allow discrimination among selected irritant chemicals.

The current review examines challenges to the predominant paradigm of two decades ago, with an emphasis on human psychophysics. Acknowledged up front is that psychophysics rarely yields mechanistic answers but rather is a hypothesis-generating tool relative to biology. The basic premise is that there may be significant qualitative chemesthetic specificity within the nasal trigeminal system. The data reviewed should be viewed in the context of parallel findings in molecular biology, electrophysiology, and functional central nervous system imaging (reviewed in the accompanying symposium chapters). Qualitative psychophysical data are considered in the following categories: qualitative discrimination of irritants, interstimulus interactions, stereospecificity, and finally the "cutoff" phenomenon in quantitative structure–activity relationships.

Qualitative Discrimination of Irritants

Laska and colleagues[19] exposed 20 anosmics and 50 normosmic controls to six different vapor-phase irritants equalized for total intensity. Test compounds included acetic acid, acetone, ethanol, cineole, menthol, and *n*-propanol. Subjects were asked to assign and rank the top three adjectives describing the stimuli from an extensive list and to discriminate between pairs of stimuli using an oddball paradigm. With the exception of distinguishing between acetic acid and menthol vapors, the two groups performed similarly on the discrimination task. In addition, most of the compounds elicited similar descriptive profiles between the two groups. (One exception was acetic acid, which elicited significant taste descriptors in the normosmic group only.) The authors concluded that significant qualitative data were being conveyed by the trigeminal system in the absence of olfactory input.

In a follow-up study, Laska[20] compared the nasal trigeminal discrimination performance of 100 elderly (65–88 years) and 100 young (23–36 years) subjects. The investigators found consistent use of qualitative descriptors across age groups, with the elderly performing discrimination tasks with a slight decrement compared to younger subjects. They concluded that the ability for trigeminal discrimination is mostly conserved over the lifespan.

Interstimulus Interactions

Brand and Jacquot[21] studied repeated nasal vapor-phase exposure to allyl isothiocyanate (mustard oil) in 60 subjects. Subjects rated irritation intensity by using the method of magnitude estimation. The effect of previous stimulation varied according to the interstimulus interval, with short (less than 2 min) interstimulus intervals producing sensitization whereas long (greater than 3 min) interstimulus intervals produced desensitization. They observed that the effects of repeated mustard oil stimulation are time dependent, consistent with the effects of repeated capsaicin exposure.

Jacquot *et al.*[22] studied repeated vapor-phase exposures to allyl isothiocyanate and acetic acid in 12 subjects. Subjects rated irritation intensity by using the method of magnitude estimation. Similar to repeated allyl isothiocyanate exposure, repeated acetic acid exposures produced self-desensitization. However, pretreatment with acetic acid decreased the irritancy of allyl isothiocyanate, whereas the reverse was not the case. The authors concluded that interstimulus interactions between allyl isothiocyanate and acetic acid involved asymmetrical desensitization, by an unknown mechanism.

Geppetti and colleagues[23] studied nasal irritation ratings of liquid-phase citric acid and hypertonic saline before and after multiday capsaicin application to the nasal mucosa. A total of 34 subjects rated irritation intensity using visual analog scales. Over the course of pretreatment there was a significant reduction in capsaicin-induced nasal irritation (i.e., self-desensitization). Further, the investigators found a significant reduction in citric acid irritancy after capsaicin treatment (cross-desensitization) but no reduction in irritancy of hypertonic saline (i.e., selective cross-desensitization).

Stereospecificity

Studies utilizing *R*- and *S*-enantiomers of nicotine have shown stereospecific effects in terms of both psychophysical (irritant) rating and electrophysiological response, implicating the operation of a specific receptor (see below).[24,25] Electrophysiological studies comparing the ensemble response of the ethmoid nerve in rats to nicotine-induced (versus cyclohexanone-induced) irritation showed a selective decrease in response to the former compound after administration of nicotinic receptor blocking agents, likewise suggesting the operation of a specific receptor mechanism.[26]

Theurauf *et al.*[24] studied 18 healthy volunteers, 27–45 years of age. Subjects were exposed nasally to vapor-phase *R*(+)- and *S*(−)-nicotine. Investigators documented trigeminal detection, suprathreshold irritation rating, and the negative mucosal potential. Of note, the potency for all assays was *S*(−)-nicotine > *R*(+)-nicotine. The authors took these results to be consistent with the action of a stereoselective nicotinic acetylcholine receptor in the human nasal mucosa.

Switching for a moment to respiratory behavior studies in rodents (a predictor of human sensory irritation), two such studies have looked at a class of nonreactive VOCs with sufficient molecular complexity to include asymmetric carbons. Nielsen *et al.*[27] exposed BALB/c mice to two α-pinene enantiomers, (+) and (−). Investigators measured disruptions (slowing) of breathing patterns, concluding that (+)-α-pinene was a more potent sensory irritant than (−)-α-pinene. Kasanen and colleagues[28] performed a similar experiment in OF1 and NIH/S mice using two α-pinene and two β-pinene enantiomers, (+) and (−). They found that both (+)-α- and (+)-β-pinene were more potent sensory irritants than their (−) equivalents. Both groups of investigators concluded that they had observed stereospecific irritancy consistent with differential binding of pinene enantiomers to a specific membrane receptor.

Structure–Activity Relationships

Cometto-Muniz and co-workers[29] studied the psychometric function for eye irritation detection in homologous *n*-alcohols (carbon chain length, 9–11) at different flow rates and durations of exposure. Experiments involved saturated vapor from the neat (undiluted) chemicals in a three-alternative, forced choice paradigm, with 20 trials per chemical–flow rate–duration combination. Subjects included nine normosmics, eight of whom were nonsmokers. Whereas earlier experiments had confirmed increasing irritant potency within various homologous series with increasing carbon chain length (up to 8), the investigators found that detection probability fell off above a carbon chain length of 9. Further, with carbon chain lengths greater than 10, increasing flow rate failed to increase detectability. Finally, heating the vapor from room to body temperature (to compensate for decreasing volatility) did not consistently improve detectability. Similar data were found for homologous acetates, alkylbenzenes, ketones, and carboxylic acids.[30–32] The authors concluded that they had observed a cutoff phenomenon in eye irritation, indicative of a possible sterically hindered receptor site. They further calculated that the critical (unfolded) molecular length was between 18 and 19 Å.[29]

Conclusions

Psychophysical studies can be valuable for generating hypotheses about biological mechanisms. Studies have suggested there may be significant qualitative encoding in the nasal trigeminal system which is conserved, in some cases, up to the cortical level. Interstimulus studies have yielded complex data, including self-sensitization, self-desensitization, and cross-desensitization (often asymmetric). These data will most likely be explained, in time, at a peripheral—if not molecular—level. The findings of stereospecificity and the cutoff phenomenon for nonreactive VOCs suggest a paradigm involving, rather than nonspecific membrane interactions, interaction with one or more VOC receptors, however broadly tuned. Notwithstanding this eventuality, physico–chemical modeling will most likely continue to highlight the importance of transport phenomena in determining chemesthetic potency.

The combination of receptor diversity and qualitative discrimination raises questions about the intervening "wiring diagram." Since we know there are nerve fiber subpopulations that differ not only in their degree of

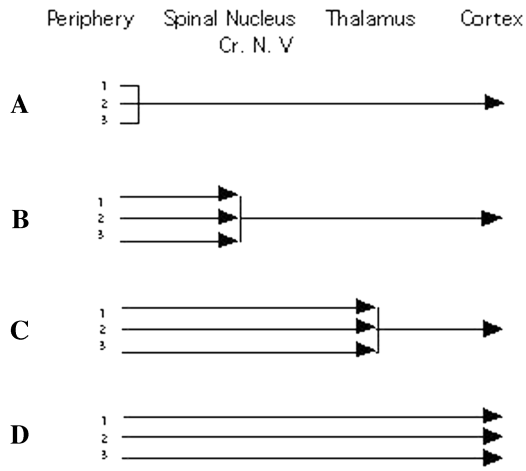

Figure 1. Schematic representations of alternative models for qualitative information flow in the trigeminal system. Numbers (1, 2, and 3) represent specific receptor expression patterns in afferent trigeminal fibers. (**A**) Fibers with relatively homogeneous representation of receptors peripherally; (**B** and **C**) fibers with distinct receptor populations converge before reaching the cortex; (**D**) fiber specificity is maintained from the periphery to the sensory cortex. Representation **A** is inconsistent with the results of the single-fiber electrophysiological and *in vitro* calcium imaging studies reviewed in the text. However, current empirical data do not support a single alternative among patterns **B** to **D**. Similar receptor expression patterns on different fibers (i.e., C- versus A-delta) may also give rise to qualitatively distinct percepts.

myelination but also in their expression of nociceptive ion channels, it is possible that this information is conserved, either through encoding or a "labeled line" arrangement, as it flows centrally (Fig. 1). In contrast to the human psychophysical data reviewed above, animal behavioral data bearing on this question give scant support. Specifically, Silver *et al.*[33] conditioned salamanders to avoid either amyl acetate or D-limonene but to tolerate cyclohexanone and butanol. After olfactory nerve sectioning, the animals could no longer discriminate between the paired odorants presented at concentrations that produced an equal (ensemble) electrophysiological response in the trigeminal nerve. Overall, the level of perceptual specificity in the trigeminal system—and the neurobiological substrate for such specificity—has yet to be fully explored.

Conflicts of Interest

The author declares no conflicts of interest.

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