I. INTRODUCTION

During the early part of the 19th century, there was considerable debate regarding whether the sense of smell was mediated by the first cranial nerve (CN I, the olfactory nerve) or the fifth cranial nerve (CN V, the trigeminal nerve). Although Sir Charles Bell believed that olfaction was subserved by CN I (Bell, 1812), he erroneously thought that CN I and CN V fibers were united for a portion of their projection, as indicated in his 1811 classic *Idea of a New Anatomy of the Brain* (Bell, 1966). Francois Magendie, Bell’s chief French rival and the primary proponent of the theory that CN V mediated olfaction, published his major arguments in 1824, along with a series of flawed physiological animal experiments that he touted as demonstrating his point (Magendie, 1824).

Magendie’s conclusions received little confirmation from others, and reports soon appeared supporting Bell’s contention that CN I mediates olfactory function. For example, in 1826 Eschricht noted that persons without olfactory nerves or with degenerate nerves were anosmic. Cruveilhier (1829) communicated a case to the Anatomical Society of Paris (of which he was President) in which a fungus of the dura matter had produced damage to the optic chiasm and had destroyed the olfactory nerves and sectors of the anterior cerebral lobes, but left the trigeminal nerves intact. This individual was both anosmic and blind. Vidal (1831) subsequently reported to the same society a case of an anosmic blind person who, at autopsy, had a tumor that destroyed the optic and olfactory nerves, but not the trigeminal ones. Two years later, Bishop (1833) reported on a patient with paralysis of the trigeminal nerve with normal ability to smell, and Shaw (1833) wrote a scathing critique of Magendie’s earlier experiments, pointing out why they were invalid.*

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*To place these observations in historical context, it should be noted that it was not until 1847 that Todd and Bowman reported that a sector of the epithelium on the upper concha differed in appearance from the rest of the nasal mucosa (Todd and Bowman, 1847). The different cell types within the olfactory epithelium were first described in 1855 (Eckhard, 1855; Ecker, 1855). The first descriptions and illustrations of true olfactory receptor cells and their cilia were published in 1856 (Schultz, 1856). An excellent review of these and other early studies is provided by Zippel (1993); see, also the Introduction and Chapter 8 of this volume.
Today we know that the qualitative sensations of smell are mediated by CN I; however, we also know that most, if not all, odorous chemicals have the propensity to stimulate, directly or indirectly, free nerve endings of CN V located within the lining of the nasal vestibule and nasal chambers, producing such sensations as irritation, tickling, burning, warming, cooling, and stinging. These sensations, which often serve to avert the organism away from harmful sources of stimulation, are classified by some as a component of the "common chemical sense", a term first used by Parker (1912) to describe the general chemical responsiveness of mucosal and epithelial tissue mediated via free nerve endings from a number of different nerves.

In addition to serving chemosensory functions, CN V fibers within the nasal vestibule mediate the tactile sensations of temperature and pressure, including the perception of nasal airflow during breathing (Burrow et al., 1983; Cauna and Hinderer, 1969). Importantly, CN V stimulation can reflexively influence cardiovascular responses (e.g., heart rate and blood pressure), respiration rate, nasal engorgement, epinephrine secretion, nasal secretion, and sneezing (Alarie, 1966; Allen, 1929; James and Daly, 1969, 1972; Kratschmer, 1870), and there is evidence that the trigeminal and olfactory systems interact centrally. For example, olfactory and trigeminal pathways converge on the same neural elements within the mediodorsal nucleus of the thalamus of the rat; blocking the trigeminal pathway enhances odor-induced activity in the nucleus (Inokuchi et al., 1993). Lesioning or reversibly blocking the rabbit trigeminal ganglion inhibits olfactory bulb activity (Stone et al., 1968). Electrical stimulation of the trigeminal nerve decreases bulbar activity (Stone, 1969), a phenomenon that has also been reported for electrical stimulation of the vagus nerve (Garcia-Diaz et al., 1984). Interestingly, CN V may also modulate the activity of olfactory receptor cells within the neuroepithelium via a local axon reflex associated with the release of substance P (SP) (Bouvet et al., 1987).

In this chapter, I (1) review basic aspects of the anatomy and physiology of the intranasal trigeminal system, with an emphasis on humans, (2) describe basic characteristics of human trigeminal chemosensory processing, and (3) present data from psychophysical studies that demonstrate CN V interactions with CN I-mediated chemoreception. The reader is referred elsewhere for more general reviews on this and related topics, including the complex relationships between the trigeminal system and autonomic processes in general (DeLong and Getchell, 1987; Eccles, 1990; Keverne et al., 1986; Tucker, 1963; Walker et al., 1990; Widdicombe, 1986).

II. ANATOMY AND PHYSIOLOGY OF THE INTRANASAL TRIGEMINAL SYSTEM

In the human, sensory nerve endings from branches of the trigeminal nerve are found in the epithelia of the nose and sinuses, the oral cavity, the eyelids, and the cornea (Fig. 1). The anterior and lateral portions of the nasal cavity are innervated by the lateral and medial nasal branches of the ethmoidal nerve, which is derived from the nasociliary branch of the ophthalmic division of CN V arising from the trigeminal ganglion (also called the Gasserian or semilunar ganglion). This nerve enters the nasal cavity via the anterior ethmoidal foramen near the lateral margin of the cribiform plate. The posterior portion of the nasal cavity is innervated by the nasopalatine nerve, one of the four nerves that branch from the sphenopalatine ganglion. This nerve contains parasympathetic postganglionic fibers from the sphenopalatine ganglion, sympathetic postganglionic fibers from the sympathetic ganglia in the neck, and sensory fibers from the maxillary nerve that traverse the sphenopalatine ganglion.

*A number of studies suggest that the nasal mucosa also receives some sensory fibers from the facial (CN VII), vagus (CN X), and upper thoracic spinal nerves, although their role, if any, in chemoreception is obscure. It has been suggested that these pathways may explain referred pain and headaches due to nasal disease (Eccles, 1982).
Intranasal Trigeminal Chemoreception

Figure 1  Primary branches of the trigeminal nerve that innervate the nasal and oral cavities. (Reprinted with permission from Silver, 1987.)

Developmentally, the trigeminal nerve is well formed in utero (Gasser and Hendrickx, 1969; Hogg, 1941). Indeed, the perioral areas supplied by the mandibular and maxillary divisions are the first embryonic regions to respond to cutaneous stimulation (circa 7.5 weeks). The ophthalmic division can be observed at 4–5 gestational weeks and is presumed to be functional by 10.5 weeks (Brown, 1974; Humphrey, 1966; Streeter, 1908). Not surprisingly, trigeminal reactivity to chemical stimulation is present at birth. Thus, when the nares of newborn infants (ranging in age from 16 to 131 hr) were confronted with vials containing either cotton or ammonium hydrochloride, they turned away from the side of the ammonia on 64% of 304 trials (Rieser et al., 1976).

A number of fiber types are found within each of the branches of the trigeminal nerve. In the case of the infraorbital nerve of the rat, both myelinated and unmyelinated axons are present, with myelinated ones ranging from 0.8 to 14.9 μm in diameter and unmyelinated ones ranging from 0.3 to 1.5 μm in diameter (Jacquin et al., 1984). More unmyelinated than myelinated axons are found in the ethmoidal nerve, with the preponderance of fibers ranging from 2 to 6 μm in diameter (Biedenbach et al., 1975).

Immunocytochemical studies demonstrate that fine unmyelinated C-fibers that innervate the nasal cavities contain SP and, in many cases, associated calcitonin gene-related peptide (Finger et al., 1990). Physiological studies suggest that unmyelinated C-fibers are responsible for irritative reactions in the nasal and respiratory passages, as well as in the body skin, although small
myelinated A-delta fibers may also be involved (Jancso et al., 1967; Lundblad et al., 1983). Silver et al. (1985) noted that chronic administration of capsaicin (which depletes, to a large degree, SP from fine unmyelinated afferents) eliminated or severely reduced trigeminal nerve responses to chemicals in rats, suggesting that the small unmyelinated and possibly some myelinated fibers subserve trigeminal pain reactions. Other classes of peptidergic fibers (e.g., ones that contain vasoactive intestinal peptide and luteinizing hormone releasing hormone) are also found within the nasal epithelium, although their role in chemosensory mediation is not defined (Silver et al., 1985).

Although a few nonolfactory nerve fibers have been observed extending to the epithelial surface of the nasal epithelium (see, for example, Lundblad et al., 1983), Finger et al. (1990), using data from electron microscopy studies, report that the vast majority of CN V free nerve endings terminate within the lamina propria, at least in amphibia and rodents. Nevertheless, they observed a few trigeminal fibers that terminated within 1 μm of the epithelium’s surface, just below the tight junctions. Finger et al. point out that for volatile chemicals to stimulate these nerve endings, they must (1) pass into the nasal cavity, (2) partition into and diffuse through the mucus, and (3) cross the epithelial cell membranes and/or intercellular tight junctions. Since most trigeminal stimulants are lipid soluble, such transit is likely.

The nature of the receptor processes on the cell membranes that respond to chemicals is poorly understood, although several mechanisms have been proposed. Eccles (1990), for example, suggests that menthol directly influences the trigeminal afferent membranes by altering calcium conductance (Eccles, 1990). Jancso and associates have proposed that capsaicin stimulates a sensory “irritant receptor” on trigeminal membranes in the same fashion that this agent influences other nerve endings (see Jancso, 1960; Jancso et al., 1967). Steranka et al. (1987) argue that some trigeminal stimulants act by producing bradykinin in the damaged tissue and that the bradykinin subsequently binds to receptors on the free nerve endings to produce the stimulation.

III. PERCEPTION OF INTRANASAL TRIGEMINAL STIMULATION: HUMAN PSYCHOPHYSICAL AND PHYSIOLOGICAL STUDIES

Numerous studies have sought to determine the responses of volatile chemicals on the trigeminal system of humans. Such responses fall into three main categories: (1) changes in respiration, nasal secretion, and other physiological measures to chemosensory stimulation; (2) induction of perceptual qualities, such as cooling, burning, irritation, and pain; and (3) alterations in psychophysical measures of CN I-mediated odor perception. In this section, I review studies that (1) examine the propensity of chemicals to produce nonolfactory intranasal sensations, (2) compare the buildup of suprathreshold intensity as a function of stimulus concentration in both olfactory and trigeminal systems, and (3) present evidence that interactions between the trigeminal and olfactory systems occur at the perceptual level.

A. Trigeminal Stimulants and the Search for “Pure” Odorants

For many years investigators have sought to identify chemicals that produce “pure” olfactory sensations, i.e., odorants uncontaminated by trigeminal activity. Such agents would be extremely useful in human olfactory research, since they would allow for the psychophysical investigation of CN I without potential confounding influences from CN V. In light of this quest, it is of interest that a number of early workers simply assumed that a rather clear distinction could be made between “pure” odorants and more “penetrating” ones, i.e., ones that produce tactile sensations. A case in point is Zwaarademaker (1925), who felt that the majority of essences, resins, and pitches fell into the “pure” odorant class.
Despite the attractiveness of this concept and the acute observations of many such workers, recent studies throw into question such a simple dichotomy of odorants, suggesting that even clean air can produce some intranasal trigeminal sensation, depending on its flow rate, temperature, and degree of humidification (Doty et al., 1978; Eccles, 1990). Nevertheless, as indicated in detail below, it is clear that some chemicals produce much less trigeminal stimulation than others, and that at low concentrations and flow rates some agents likely produce little or no trigeminal activity (or at least no more trigeminal activity than that produced by inhalation of clean air).

Several major attempts to identify "pure" olfactory stimulants were made in the first third of this century. Thus, three years before Allen's (1928) classic ablation study that identified the nasociliary and maxillary nerves as the source of odor-induced respiratory and cardiovascular responses in dogs, von Skramlik (1925) listed nearly 50 "pure" odorants, as inferred from the inability of five subjects to localize them to the side of the nose to which they were presented. Among these odorants were anethole, cadinene (juniper), eugenol, geraniol, indole, limonene, phenyl ethyl alcohol, pinene, skatol, and terpineol. Examples of "impure" odorants reported by von Skramlik were ones that produced smell + sweet sensations (bromoform, chloroform, ethyl chloride, iodofrom, nitrobenzol), smell + sour sensations (acetic acid, butyric acid, propionic acid, and valerianic acid), smell + cool sensations (camphor, eucalyptol, menthol, phenol, safrol), smell + warm sensations (ethanol, pentanol, propanol), and smell + painful or prickly sensations (acetone, acetic acid, ammonia, bromine, chlorine, formic acid, iodine, nicotine, pyridine, SO2, thiophene, toluol, and xylol).

In 1929, Allen performed a series of human experiments to examine the influences of a number of volatile chemicals on cardiovascular responses. In one phase of this work, he described the responses of an anosmic college student to various inhaled chemicals. This student's anosmia resulted from a fall from a telephone pole, which produced a severe skull fracture and paralysis of the left rectus lateralis eye muscle. Although the student reported being unable to smell any of the stimuli, he indicated that a number produced clear intranasal or intraoral sensations. As described by Allen (p. 625),

Fresh cat's urine was not detected, but old decomposed cat's urine, possessing a trace of ammonia, was said to produce a different sensation than a strong concentration of ammonia. . . . Pyridin was described as a taste sensation coming from the back of the throat and tongue. Peppermint caused a cooling sensation in the nose and ether a disagreeable burning sensation appearing quickly. On the other hand, chloroform elicited a pleasant sensation in the nose. Formalin, described as a tickling sensation in the nose, was a long time in appearing. A weak concentration of acetic acid or ammonia produced a burning sensation in the nose and throat, which would have resulted in a movement of the head if inhalation had continued longer. Very singularly, the subject could inhale oil of mustard for a considerable length of time without any discomfort if the cone was held 4 or 5 cm. from the nostrils. In fact, the change in respiration appeared before the sensation was detected.

Importantly, menthol, eucalyptus, camphor, peppermint, ether, chloroform, and benzol, as well as weak concentrations of the strong irritants formalin, acetic acid, and ammonia, produced augmented inspirations without altering respiration rate per se. Inhalation of the oils of bergamot, cloves, orange, lavender, rose, and wintergreen, as well as asafetida, butyric acid, xylol, and fresh cat's urine, resulted in no such changes.

*It is of interest that Allen reported that his study was a replication and expansion of observations made earlier by Kratschmer (1870) and Beyer (1901) on this topic.
It is noteworthy that the stimuli reportedly detected by this anosmic student corresponded well to those classified by von Skramlik as being "impure" odorants (e.g., pyridine, chloroform, acetic acid, ammonia, menthol, peppermint, and formalin), providing at least rough validation of their nonolfactory effects. Similarly, a number of the chemicals that this study reported as not influencing respiration or being detected by the subject were the same as some of von Skramlik's "pure" olfactants [e.g., eugenol (cless)].

Although in the years following these studies several other investigators commented on stimuli that reportedly produced no trigeminal stimulation (e.g., Elsberg et al., 1935), little psychophysical research was performed on this topic until 1975, when 14 anosmics were presented with 31 chemicals in sniff bottles and asked if any intranasal sensations were detected (Doty, 1975). Eleven of the chemicals (35%) were reported by these subjects not to be detectable: anethole, benzyl acetate, eugenol, geraniol, heptane, heptyl alcohol, hexanoic acid, nonane, octane, 2-phenyl ethyl alcohol, and α-terpineol. Again, most of these chemicals fell within the set that von Skramlik reported as being "pure" olfactants.

In contrast to this finding, however, were the results of a subsequent and more extensive study of 47 chemicals [which included the 31 chemicals used in the Doty (1975) study] which incorporated a forced-choice detection paradigm (Doty et al., 1978). In this experiment, three groups of subjects (n = 15/group) were evaluated: (1) anosmics lacking CN I, but not CN V, nerve function; (2) normals asked to rate only intranasal CN V sensations (termed the trigeminal focus group; and (3) normals asked to rate the overall odor experience. During testing, each subject was blindfolded and, on a given trial, was presented with two sniff bottles, one after the other in random order. One bottle contained a blank (propylene glycol) and the other an undiluted odorant. Each subject was asked to identify which of the two bottles seemed strongest. If reliable detection occurred, the subject was asked to rate the stimulus' intensity, pleasantness, coolness, warmth, and presumptive safety on a series of anchored rating scales.*

This study, unlike the previous one, found that nearly all (45/47, or 96%) of the chemicals were detected by at least some of the anosmics. Although differences in the rated intensities given to the stimuli were present among the three groups (e.g., the normal subjects consistently rated the stimuli as much stronger than did the other two groups), the relative rankings of the intensity responses were similar (r's ranging from 0.92 to 0.97). The pleasantness and presumed safety ratings were inversely related to the ratings of perceived intensity in all three groups. The major point of significance of this study was its conclusive demonstration that anosmics and normal subjects could detect nearly all the chemicals presented to them via nonolfactory means when the testing was performed in a forced-choice format, thereby throwing into question the conclusions of the previous psychophysical studies on this topic (where subjects were simply asked whether or not they smelled something or whether they could correctly localize the side of nasal stimulation).

The mean intensity ratings for each of the 47 chemicals provided by the anosmic, trigeminal focus, and normal subjects in the Doty et al. (1978) study are presented in Table 1, along with the proportion of subjects within each group who detected them. It is of interest that only one chemical, vanillin, was not detected by at least one subject from the anosmic or trigeminal focus groups, and that a number of chemicals reported to be "pure" odorants by von Skramlik

*We also performed structure-activity studies to determine whether we could predict the degree of trigeminal stimulation of the chemicals. The use of 11-13 readily available and computer-derived molecular descriptors in linear learning machine pattern recognition analyses separated the stimuli correctly into four discrete intensity classes. A multiple linear regression equation based on such descriptors proved successful in predicting the trigeminal intensities of 12 chemical stimuli similar in structure to members of the original stimulus set (r = 0.80 between predicted and observed intensities).
<table>
<thead>
<tr>
<th>Compound</th>
<th>Anosmic group</th>
<th>Trigeminal-focus group</th>
<th>Normal group</th>
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<tr>
<td></td>
<td>Proportion detecting</td>
<td>Intensity</td>
<td>Proportion detecting</td>
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and others (e.g., anethole, eugenol, geraniol, indole, limonene, phenyl ethyl alcohol, and turpentine) were detected (albeit as weak) by at least a few subjects from the anosmic and trigeminal focus groups.

An electrophysiological study by Silver and Moulton (1982) adds credence to the validity of these findings. Thus, these investigators found that the relative magnitude of whole-nerve recordings from the ethmoid branch of nine rats correlated very strongly \( r = 0.975 \) with the intensity ratings from the Doty et al. study for the nine compounds they evaluated. The magnitude of this correlation is striking, particularly in light of the fact that responses of a quite different nature were being compared across species from different mammalian orders.

B. Threshold Perception of Trigeminal Stimulation

The human trigeminal system appears to be less sensitive than the human olfactory system to low concentrations of a broad array of chemicals. For example, one study using sniff bottles found that detection thresholds of anosmics for methyl ethyl ketone and furfural were, on average, two log concentration units higher than detection thresholds for these compounds in normal subjects (Doty, 1975). In another study, which incorporated air-dilution olfactometry, nasal irritation thresholds for acetic acid, propionic acid, and amyl acetate were found to be 30, 50, and 200 times higher, respectively, in four anosmics than in 16 normal subjects (Walker and Jennings, 1991).*

Additional support for greater olfactory than trigeminal sensitivity to volatile chemicals comes from animal psychophysical studies. Thus, Henton et al. (1969) found psychophysical thresholds to amyl acetate, butyl acetate, and butyric acid to be one-half to a full log unit (relative to saturation) higher in pigeons whose olfactory nerves had been severed than in intact pigeons. Since these authors also reported gradual improvement in postoperative detection performance and since the olfactory nerve of pigeons is capable of remarkable regeneration, Walker et al. (1979) repeated this study using amyl acetate and pigeons in which large segments of the olfactory nerves had been removed, preventing their regeneration. Postoperative thresholds were more than 2.5 log units higher than preoperative thresholds, and no improvement over repeated postoperative tests was observed.†

1. Suprathreshold Perception of Trigeminal Stimulation

Several lines of evidence suggest that the suprathreshold buildup in trigeminal sensation across increasing stimulus concentrations may be more rapid for the trigeminal than for the olfactory (or olfactory + trigeminal) nerve(s), conceivably reflecting CN V's involvement in nociception.

*The results of one study (Cain, 1974) appear to be at odds with these conclusions. Thus, while propanol detection thresholds were reportedly higher in the trigeminal-deficient nostril of two patients with unilateral CN V destruction secondary to the removal of acoustic neuromas, these differences were not significant and no such differences were found for n-butanol thresholds. However, these subjects also had unilateral facial nerve (CN VII) paralysis, unilateral deafness (CN VIII), and unilateral loss of vestibular sensitivity (CN VII). Thus, one or more of these factors may have influenced the sensitivity of the "normal" nasal chamber, in light of studies of the taste system that demonstrate that unilateral anesthetization of the chorda tympani nerve (CN VII) increases the perceived intensity of tastants presented to the circumvallate papillae (CN IX). Interestingly, tastants presented to the circumvallate papillae on the side opposite to the blocked nerve elicit the greatest increase in the postblock perceived intensity (Lehman, 1991).

†It is conceivable that species differences in the relative sensitivity of the trigeminal and olfactory nerves to chemicals are present. In the early 1960s, Tucker compared the sensitivity of CN I and CN V to a number of odorants in the gopher tortoise (Tucker, 1963). For most compounds, CN I was more sensitive than CN V, although, in a few instances, the reverse was true (e.g., benzylamine). Tucker also demonstrated that electrical stimulation of CN V resulted in vascular changes within the mucosa and in the flow of nasal secretions.
or mutual inhibitory influences of CN I and CN V on one another (see next section). For example, Doty (1975) found the average exponent of power functions fitted to magnitude estimation data from anosmic patients to be larger than those fitted to analogous data from normal subjects for both methyl ethyl ketone (0.35 vs. 0.30) and furfural (0.55 vs. 0.45), although these differences were not statistically significant. Cain (1976) reported, for the odorant n-butanol, that the function relating perceived irritation to stimulus concentration is steeper than that relating perceived odor to stimulus concentration in normal subjects. Similarly, Murphy (1987) points out that the power function exponent for CO₂ (a strong irritant at high concentrations) is 1.2, a value much larger than those observed for odorants commonly used in olfactory research (e.g., Berglund et al., 1971; Doty, 1975).

C. Psychophysical Interactions Between CN I and CN V

In light of the physiological interactions between CN I and CN V mentioned earlier, one might expect that stimulation of CN V might alter sensations derived from stimulation of CN I. There is some mention of this in the early literature. Thus, as noted by Cain and Murphy (1980), it was reported by Alexander Bain in 1868 that “if a current of carbonic acid accompanies an odour, the effect (odour) is arrested.” In 1930, Katz and Talbert reported that the irritation property of some odorants with both odor and irritative properties predominates at high concentrations, suggesting that CN V stimulation is masking CN I-mediated perception.

More refined support for this concept comes from a study by Cain and Murphy (1980). These investigators had eight subjects judge the perceived magnitude (i.e., intensity) of four concentrations of n-amyl butyrate, four concentrations of carbon dioxide, and all 16 combinations of these mixtures. The stimuli were presented to one nostril only, and magnitude estimates were made using the method of magnitude estimation (where subjects assign numbers relative to the perceived magnitude of the stimuli). The subjects first judged the magnitude of the overall sensory experience, and then of the odor and irritative components. A similar experiment, in which the CO₂ was presented to one nostril and the odorant to the other, was also performed using 10 subjects. Overall, the perceived magnitude of the n-amyl butyrate appeared to be suppressed by the CO₂, and vice versa (i.e., the magnitude of irritation was depressed by some concentrations of n-amyl butyrate), even when the odorant and irritative stimuli were presented to separate nares. This suggested to these authors that the locus of interaction was in the central nervous system.

IV. SUMMARY

In this chapter, basic aspects of the anatomy, physiology, and chemical responsiveness of the human intranasal trigeminal system were reviewed. It is apparent that (1) the nasal trigeminal system is less sensitive to odorants than the olfactory system, (2) very few, if any, odorants fail to stimulate CN V in at least some individuals at high odorant concentrations, and (3) complex interactions exist between CN I and CN V which, under appropriate circumstances, can be demonstrated perceptually. Potentially, CN V contributes to odor perception in at least four ways:

*Not all data are in agreement with this notion. Thus, Cain (1974) examined the perceived magnitude, as well as the time course of adaptation, to suprathreshold concentrations of propanol, butanol, and n-butyl acetate in each nostril of patients with unilateral CN V destruction secondary to the removal of acoustic neuromas. For propanol and butanol, the plotted slopes of the log-log functions relating odorant concentration to perceived intensity were very similar for the normal and trigeminal deficient sides of the nose, although the absolute magnitude of the reported sensations was greater in the normal sides.
(1) by modifying nasal patency, nasal secretion, and respiratory processes; (2) by influencing olfactory bulb or other olfactory system activity centrally via centrifugal mechanisms; (3) by altering local axon reflexes and release of neurohormones or transmitters; and (4) by providing direct chemosensory input in addition to that provided by CN I. Clearly, the intranasal trigeminal system is of interest not only because it responds to a number of chemicals, but because it may play a role in modulating elements of odor perception, per se.

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Intranasal Trigeminal Chemoreception


