Int Arch Occup Environ Health (2002) 75: 305–313
DOI 10.1007/s00420-002-0315-7

ORIGINAL ARTICLE

Thomas Hummel · Andrew Livermore

Intranasal chemosensory function of the trigeminal nerve and aspects of its relation to olfaction

Received: 15 June 2001 / Accepted: 8 December 2001 / Published online: 2 March 2002

Abstract ***Objectives***: The review outlines characteristics of the intranasal trigeminal chemosensory system. In addition, it provides selective comparisons of the trigeminal and olfactory systems, the two of which interact at multiple levels. ***Results and Conclusions***: This interaction between the trigeminal and olfactory systems is an important determinant of sensations of odor. Further, it appears to change as a result of aging and disease. Thus, the interaction between the olfactory and trigeminal systems is not straightforward and may be difficult to predict, but it has a powerful influence on the perception of odors.

Keywords Irritation · Chemosensory · Electrophysiology · Human · Psychophysiology

Introduction

What is commonly known as the sense of smell is, in fact, composed of multiple sensations, predominantly mediated by two independent neural systems, the olfactory and somatosensory (trigeminal) systems. Few chemosensory stimulants produce exclusively olfactory, or trigeminal sensations (i.e., stinging, burning, or pungent), the vast majority possessing characteristics of both odor and irritation. A review of 47 odorants [29] revealed that only two stimuli, vanillin and decanoic acid, could not be detected by anosmic individuals, and were assumed to possess no trigeminal activity at the undiluted concentrations that were used. In contrast, only one stimulant, carbon dioxide (CO_2), has been found to activate selectively the trigeminal nerve with little or no concomitant olfactory stimulation [12, 33, 70].

It is interesting that while both systems contribute to overall sensory experience, they appear to have evolved for different purposes. The primary function of the intranasal trigeminal system is to act as a sentinel of the airways where they reflexively stop inspiration to prevent inhalation of potentially life-threatening substances [97]. This reflex is so well developed that it is used to investigate intranasal chemosensory mechanisms [37, 48, 65]. In contrast, it has been suggested that olfaction may act as a non-verbal retrieval mechanism for the memory of a particular situation and the emotional response associated it [69].

Basic anatomy and physiology of the intranasal trigeminal system

The nasal cavity is innervated by the ophthalmic and maxillary branches of the trigeminal nerve [79]. Branches of the ophthalmic nerve (anterior ethmoidal nerve, infraorbital nerve) innervate the anterior portion of the nasal cavity. The posterior part of the nasal cavity is innervated by fibers of the maxillary branch (posterior superior medial nasal nerve, nasopalatine nerve). Psychophysical [113] and electrophysiological data [58] indicate that an area of increased trigeminal chemosensitivity might be found at the anterior third of the nasal cavity.

Through different receptive structures, trigeminal afferents mediate sensations of touch, pressure, temperature, and nociception [64, 96]. In terms of chemical stimulation it appears to be especially important that nociceptors innervating the mucosa, unlike those in the skin, are not covered by squamous epithelium, giving chemical stimuli almost direct access to the free nerve endings [32]. Thus, chemical stimulation appears to

T. Hummel (✉)
Department of Otorhinolaryngology,
University of Dresden Medical School,
Fetscherstrasse 74, 01307 Dresden, Germany
E-mail: thummel@rcs.urz.tu-dresden.de
Tel.: +49-351-4584189
Fax: +49-351-4584326

A. Livermore
School of Social Sciences & Liberal Studies,
Charles Sturt University – Mitchell, Bathurst,
New South Wales, Australia

activate several receptor types. For example, gaseous CO_2 produces stinging and/or burning sensations when applied to the mucosae of the nose or eye [24]. Stinging sensations are likely to be mediated by A_{delta} fibers, whereas burning sensations are largely mediated by C fibers [85, 99, 111]. In terms of receptive mechanisms, gaseous CO_2 appears to activate chemosensory nociceptive afferents (C fibers, A_{delta} fibers) by the intracellular accumulation of protons [75, 103]. This increases a cation membrane conductance [8, 76] with slow desensitization [102]. Some of these channels are also activated by capsaicin, the hot ingredient in chili peppers [9, 19, 101]. The nociceptive specificity of CO_2 has been demonstrated in experimental animals pre-treated with capsaicin which selectively destroys nociceptive afferents (compare [98]). Nociceptive responses to CO_2 were strongly diminished when compared with untreated controls [110]. In addition, CO_2 does not seem to induce activity in mechanosensory A_{delta}- or A_{beta} fibers [102]; also, afferents activated by CO_2 do not respond to specific olfactory stimulants such as hydrogen sulfide [54, 95].

Recently, a capsaicin-gated channel has been found in small-to-medium diameter sensory afferents of trigeminal and dorsal root ganglia [16, 17]. This receptor is termed vanilloid receptor 1 (VR1), which is also activated by protons and noxious heat. Other specific mechanisms of nociceptor activation include the acid-sensing ion channel [82]. In addition, there is evidence that different nicotine enantiomers activate trigeminal afferents in a stereoselective manner [95] (see also [2]). Thus, it appears as if the "common chemical sense" [90] may allow discrimination between more chemical stimulants than has previously been assumed [80].

Recently, both electrophysiological and psychophysical measures have been used to investigate effects of chronic exposure to the chemosensory irritant acetic acid [51]. In a long-term adaptation protocol, subjects were exposed to acetic acid vapor in their home environment. Results indicated an effect from exposure to acetic acid, both at the receptor level and centrally. In contrast, responses to acetone showed little change over the course of long-term exposure to acetic acid. Thus, these data suggest that the responsiveness of the trigeminal system can be specifically desensitized, indicating the presence of specific receptive structures in the trigeminal system.

Cell bodies of trigeminal afferents lie in the gasserian ganglion. The axons project to the subnuclei of the trigeminal sensory nucleus, the spinal, principal and mesencephalic trigeminal nuclei extending from the rostral spinal cord to the midbrain. Nociceptive afferents descend in the trigeminal tract and terminate in the spinal nucleus. Chemosensory fibers from the nasal cavity have been shown to project to spinal nuclei, e.g., the subnucleus caudalis, and subnucleus interpolaris [3, 4]. Trigeminal information is relayed to the amygdala via the lateral parabrachial complex [7]. Neurons of the spinal nucleus project to the ventral posterior medial, intralaminar, and mediodorsal nuclei of the thalamus. Most ascending fibers cross to the contralateral side; however, in a way similar to the olfactory system [28], some fibers also ascend ipsilaterally [6]. From the thalamus fibers project to the primary somatosensory cortex. In addition, there is convincing evidence that trigeminal stimulation produces activation of the secondary somatosensory cortex [20, 61]. Finally, trigeminal activation leads to activity in the insular cortex [68] and the ventral orbital cortex [60, 100], with stronger right-sided activity following bilateral stimulation [43, 60]. These areas have also been shown to be involved in the processing of olfactory information, and, similarly, research indicates that the right hemisphere is involved to a larger degree in the processing of information about odors [56, 63, 89, 117, 118].

Consequences of the activation of different receptor types

While overall intensity ratings increase when stimuli are applied at intervals of fewer than 3 s [52], C fibers and A_{delta} fibers respond differently to repeated chemical stimulation. This increase is typically accompanied by the buildup of a dull and burning painful sensation characteristic of C-fiber stimulation [91]. However, the intensity of stinging sensations (mediated by A_{delta} fibers) decreases as a function of decreasing interstimulus interval [52]. The increase of burning sensations at short interstimulus intervals is not the effect of increased firing rates of C fibers [111]. In fact, at small interstimulus intervals, conduction velocity in human C fibers slows down and may even fail at intervals shorter than 1 s [94]. In contrast, responses in dorsal horn neurons increase in response to repetitive stimulation of C fibers when the interstimulus interval becomes smaller than 3 s [41]. Thus, the "wind-up" of painful sensations after repetitive stimulation may be due to central nervous summation of the input produced by stimulation of C-fiber afferents. That is, while sensations are critically dependent on temporal summation, central nervous summation phenomena occur despite the partial suppression of afferent activity. In contrast, no such summation has been reported for stinging painful sensations [1, 96]. Both peripheral adaptation and/or central habituation may eventually lead to the decrease in stinging after repetitive stimulation [40, 92].

Perceptual characteristics – thresholds

The nasal trigeminal system has been found to be less sensitive than the olfactory system (for review see [36]). As the vast majority of chemosensory stimuli activate both the olfactory and trigeminal systems, it is difficult to identify their separate contributions. To overcome this many studies have concentrated on anosmic subjects with no olfactory function. Cometto-Muñiz et al. [22] investigated thresholds for a range of homologous

alcohols, acetates, ketones and alkylbenzenes. Odor thresholds (measured in normosmic subjects) were found to be from 1.6 to 5.2 orders of magnitude lower than pungency thresholds (measured in anosmic individuals). Further, this difference was found to increase with carbon chain length. These findings are supported by a study in pigeons with lesioned olfactory nerves [115]. Thresholds of lesioned birds, presumably based on trigeminal stimulation, were found to be a half-log to 2.5-log units higher than non-lesioned animals.

A number of studies have investigated thresholds for stimulation with CO_2, which has little or no odor. Using an air flow of 5.1 l/min and a stimulus duration of 2 s, Anton et al. [5] found the mean recognition thresholds at 47% v/v CO_2. Our own work [73] has revealed that at an air flow of 8 l/min and a stimulus duration of 200 ms, mean recognition thresholds for slightly stinging sensations were at 32% v/v CO_2. It is interesting to note that the CO_2 stimuli could be distinguished from blank stimuli at much lower concentrations (23% v/v, established by means of the presentation of ascending concentrations). These pre-pain sensations may be due to low-level excitation of nociceptors [39].

Thresholds for CO_2-induced pain decrease in relation to the stimulus duration [84]. Interestingly, thresholds determined in that study were found at higher concentrations than previously reported [73]. As subjects were asked in this study [84] to report the occurrence of "painful" sensations, as opposed to "stinging" in the previous study [73]), the observed differences were interpreted in relation to the instruction presented to the subjects (compare [39]).

Another important question concerns the smallest possible concentration difference that can be discriminated, the so-called "just noticeable differences" (JNDs). Using a stimulus duration of 200 ms (50% v/v CO_2) studies have shown that a difference of 2% v/v CO_2 produced significantly different intensity ratings [84]. It has been demonstrated that JNDs depend on both stimulus concentration and duration. This study investigated JNDs in 12 subjects at stimulus concentrations of 50%, 60%, and 70% v/v CO_2, each concentration at stimulus durations of 200, 400, 800, and 1,600 ms. At a stimulus concentration of 50% v/v and a stimulus duration of 200 ms, JNDs were $1.9\% \pm 0.9\%$ v/v CO_2. For stimuli of the same concentration but at 1,600-ms duration, JNDs were $3.1\% \pm 2.6\%$ v/v CO_2. The highest JNDs of $5.5\% \pm 2\%$ v/v were observed for stimuli of 70% v/v at 1,600-ms duration. Similarly, electrophysiological recordings from the respiratory epithelium have demonstrated that it is possible to discriminate stimuli presented at concentration steps = 3% v/v [109].

Perceptual characteristics – intensity

Increases in perceived intensity with rising concentration occur more rapidly for strong trigeminal stimulants than for odor stimuli [12, 15, 25, 26]. Furthermore, the intensity of a strong trigeminal stimulant, ammonia, was shown to sum, or build up, during the course of an inhalation. In contrast, the primarily olfactory stimulus, isoamyl butyrate showed no signs of temporal summation [21].

The two systems make separate contributions to the perceived intensity of a complex stimulus. The intensity of the odor component of binary mixtures appears to be hypoadditive, indicating that the perceived intensity of a mixture is less than the sum of its components. In contrast, the trigeminal component may be additive, or even hyperadditive [26].

Using a stimulus duration of 200 ms and a 58% concentration of CO_2, Hummel and Kobal [53] showed that a 40-s inter-stimulus interval was necessary and sufficient to obtain reliable chemosensory event-related potentials CSERPs and perceptual ratings free from adaptation effects. While shorter intervals resulted in reduced ratings, longer intervals did not produce less adaptation. Kobal [70] obtained similar results with the mixed olfactory–trigeminal stimulant eucalyptol. Thus, an interval of approximately 40 s appears to be necessary to allow sufficient recovery of both systems.

Lötsch et al. [84] explored the relationship between concentration, stimulus duration and intensity systematically for CO_2. Sixteen different concentrations, ranging from 40% to 70%, were applied using four different stimulus durations, 200, 400, 600 and 1,600 ms, with a 30-s inter-stimulus interval. Participants received two sessions separated by 24 h. Pain ratings increased significantly with concentration. Interestingly, while intensity ratings did not increase with stimulus duration they became less variable. The test–retest variability of ratings was significantly higher, and hence repeatability lower with the 200-ms stimulus than with the 400 or 800-ms presentations, with 400 ms having the lowest variability. These results were paralleled by those for stimulus adaptation, with a significant degree of adaptation for the 200-ms stimulus but no evidence of adaptation at 400 or 800 ms. As the authors concluded, this implies that 400-ms presentations will give more reliable results with a lower sample size.

A similar study has been carried out using the pure olfactory stimulus vanillin [108]. Four different concentrations were presented, ranging from 7% to 84% v/v with a 200-ms stimulus duration and 40-s inter-stimulus interval. In addition to perceptual ratings, olfactory event-related potentials (ERPs) were recorded. Peak-to-peak olfactory ERP amplitudes increased, and latencies decreased, with concentration. Similarly, intensity ratings increased with stimulus concentration. While there was a significant decrease in sensitivity over the session, this was notably for the two lower concentrations, and took the form of a decrease from the first two of 16 presentations. Due to the different stimulus durations and inter-stimulus intervals, it is difficult to compare the two studies, although a couple of comparisons may be made.

At the 200-ms stimulus duration, adaptation seems to be equivalent for the two systems. When compared with

a standard high-intensity stimulus presented at the beginning of the session, overall ratings dropped to approximately 80% over the whole session.

Secondly, as both studies used a 200-ms inter-stimulus interval and magnitude estimation, it is possible to compare the increase in perceived intensity with concentration for both stimuli and thus differences in response characteristics for the two neural systems. Of course, it needs to be kept in mind that, while CO_2 and vanillin activate the two systems in isolation, within both systems different stimuli may have different response characteristics. As would be expected on the basis of previous studies, the perceived intensity of the trigeminal stimulant increases much more sharply than that for the olfactory stimulant. For vanillin, in order to increase perceived intensity 50%, from 50 to 100 estimation units, it was necessary to increase the stimulus concentration presented by approximately 45%, while for CO_2 a similar intensity increase was obtained with only a 12% increase in concentration, equivalent to a ratio of 3.75:1.

Spatial summation

Chemical stimuli are perceived as being approximately 33% more intense when inhaled through two nostrils (di-rhinal) rather than one (mono-rhinal). Cain [13] showed this with the mixed trigeminal-olfactory stimulus *n*-butyl alcohol and Garcia Medina and Cain [34] with the trigeminal stimulant CO_2. As di-rhinal stimulation involves activation of both epithelia, this may be seen as an example of spatial summation. The authors suggest, as the summation was only partial (i.e., di-rhinal intensity was less than twice as strong), an interaction in the form of masking, or suppression between the two nostrils.

Temporal summation

Kobal [70] found that the intensity of the pure olfactory stimulant hydrogen sulfide (H_2S) and the mixed stimulus linalool continued to increase with stimulus duration (i.e., showed temporal summation) up to and beyond 1,200 ms. Similarly, almost perfect temporal summation has been found for the mixed stimulus ammonia over durations of up to 4 s [21]. For example, a given stimulus of 4 s was perceived to be twice as strong as a stimulus of 2-s duration. In contrast to Kobal, the authors reported that, while temporal summation occurs over much shorter intervals for olfaction, trigeminal sensation builds over much longer periods and makes a much larger contribution to the overall perceived intensity of a mixed stimulus over time.

Hummel et al. [55] examined the differing temporal characteristics of the two systems using the mixed stimulant nicotine. In addition to odor, nicotine produces two different trigeminal sensations, burning and stinging, mediated by different fiber systems, i.e., the A_{delta}- and the C-fiber systems. Subjects rated the intensity of odor, burning and stinging on different trials (stimuli of 200-ms duration with an inter-stimulus interval of 2 min). Odor sensation appeared relatively quickly after stimulus onset, followed by stinging. These stimuli reached a maximum after 3 and 4.6 s, respectively, and then faded. In contrast, burning did not even commence until 5 s after stimulus onset and did not end until 20 s later. This striking difference in stimulus time course between systems and even within each system indicates a level of complexity and interaction even within a single stimulus, let alone between different stimuli, that needs careful consideration.

These differing relationships, in terms of thresholds, adaptation rates, and temporal and spatial characteristics, have important implications for the perception of the vast majority of chemosensory stimuli which stimulate both systems, and also for the perception of complex stimuli containing multiple active chemicals.

Relation to gender

Electrophysiological data indicate that healthy female subjects are more sensitive to trigeminal stimulants than male, i.e., women exhibit larger ERP amplitudes than men [50, 57]. Dunn et al. reported that thresholds for trigeminally induced apnea are lower in female subjects than in male [30]. These differences in chemosensory trigeminal sensitivity appear to be analogous to the olfactory system, where women typically outperform men in different aspects of olfactory function, e.g., odor identification, discrimination, and detection [14, 27, 59, 74].

Effects of aging

Compared with the olfactory system, considerably fewer data are available regarding age-related changes of trigeminal chemoreception. Elevated thresholds to trigeminal stimuli (e.g., menthol) were reported in elderly subjects [86, 87]; in addition, a steeper slope of the intensity function was found for younger adults. Stevens et al. [105] found an age-related decrease in the perceived intensity of CO_2, and Stevens and Cain [104] reported a strong age-related elevation of the threshold for transitory apnea in response to CO_2. As mentioned above, this age-related loss of trigeminal function is also seen in ERP studies [50]. Interestingly, the cross-sectional results could also be confirmed, at least in part, by individual data obtained in a single subject where trigeminal ERPs were recorded over a period of 10 years. Here an intra-individual decrease of response amplitudes to CO_2 stimuli occurred between the ages of 28 and 38 years.

Similar age-related changes have been reported for other nociceptive, pain-related processes. Specifically, responsiveness of A_{delta} fibers to nociceptive heat stimuli appears to decrease in relation to age while C fiber

function seems to be largely unaffected [18, 44]. These functional observations are also confirmed on a histological level where the number of myelinated fibers (A fibers) appears to decrease with increasing age [67, 88]. Translating all this into intranasal trigeminal function of chemosensors, this would result in decreased stinging sensations (A_{delta} fibers) while the perception of burning sensations (C fibers) would remain mostly unchanged. These observations relate closely to changes found for ERPs to intranasal trigeminal stimuli which are mostly due to the activation of A_{delta} fibers [45, 52]. Overall, this indicates that the trigeminal chemoreceptive system exhibits an age-related functional decrease, aspects of which appear to be similar to those of the olfactory system.

Olfactory–trigeminal interactions

The interaction between the olfactory and trigeminal systems has been shown to influence not only the quality of single odorants, but also the type and direction of interactions between odorants in mixtures. Before interactions between odorants can be understood, it is important to isolate the effect of odor from that of irritation, and then to look at the way in which they combine to produce a percept of the stimulus.

Trigeminal activation has been shown to influence the perception of both single odorants and mixtures (e.g., [12, 26, 71]). As mentioned above, research in the area is complicated by the fact that at sufficiently high concentrations most odors themselves produce trigeminally mediated sensations, such as cooling and pain [12, 31].

In an experiment by Cain [12], in which subjects rated pungency and odor of the stimulant butanol, the contribution of the odor component to overall sensation actually decreased with concentration, while irritation increased. Similarly, while irritation was found to contribute little to total sensation at low concentrations, its contribution increased disproportionately with concentration. In a later experiment it was found that the suppression observed between the two systems was mutual [15]. Participants received four concentrations each of CO_2 and amyl butyrate (a mixed olfactory and trigeminal stimulus) and their 16 binary mixtures. They were required to rate overall intensity, the intensity of odor and that of irritation. It was found that the odor of amyl butyrate was suppressed by CO_2 and that irritation was suppressed by some concentrations of amyl butyrate. These suppressive effects were found to occur regardless of whether the mixture was presented simultaneously to both nostrils or if a different odor was presented to each nostril, suggesting that the suppression was centrally mediated. Using mixed stimuli and a similar stimulation technique Laing and Willcox [78] found that the location of suppression, central or peripheral, varies and is dependent on the quality of the stimuli. However, it should be noted that it is difficult to interpret these interactions as occurring purely between the olfactory and trigeminal systems as, amyl butyrate being a mixed stimulus, interactions may have also occurred at the level of the trigeminal system. This is particularly the case at high concentrations of *n*-amyl butyrate where suppression of CO_2 was observed. Therefore, when investigating these effects it is desirable to use stimuli that activate each system in isolation. Such a study was performed by Kobal and Hummel [71]. When presented in binary mixtures, the trigeminal stimulant CO_2 was found to suppress the intensity of olfactory sensations produced by vanillin.

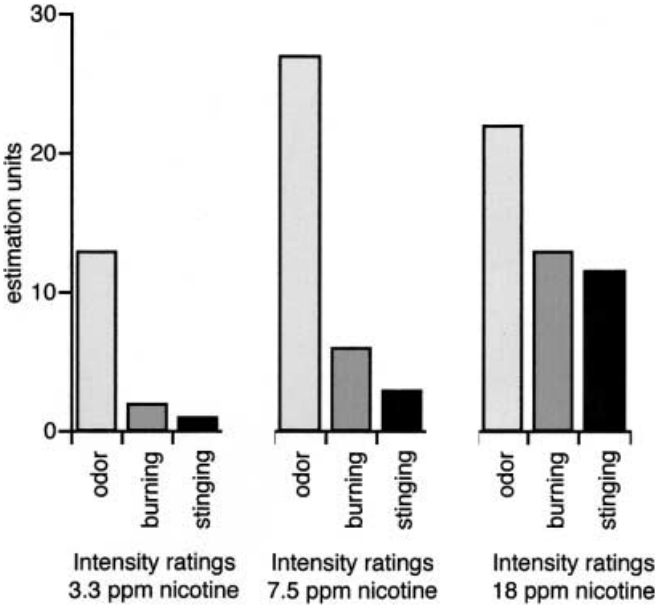

Fig. 1. Intensity ratings (means, $n = 10$) in response to stimulation with different concentrations of nicotine, separately for odor, burning, and stinging. When the highest concentration was presented stinging and burning increased significantly, but odor actually decreased (data from [55])

In an effort to assess systematically the role of olfactory–trigeminal interactions in odor perception we performed two studies, looking at interactions both within a single stimulus and between different chemosensory stimuli. In one study discussed above [55] we examined the contribution of odor, stinging, and burning to the perception of three different concentrations of the mixed stimulant nicotine (Fig. 1). At the lowest concentration the olfactory sensation predominated, with little trigeminal activation. The medium concentration produced an increase in odor and also in burning. However, when the highest concentration was presented stinging and burning increased significantly, but odor actually decreased. This suggests that there was suppression of the odor sensation by the trigeminal system at the strongest nicotine concentration – as has been suggested by Cain and Murphy [15]. These results were also reflected in the distribution of CSERPs which, at the lowest concentration, reflected an "olfactory" pattern, while at the highest concentration amplitudes reflected a "trigeminal" distribution of amplitudes.

In a later experiment [83] we examined the interaction between the two neural systems by selecting three stimuli designed to activate either the nasal trigeminal system (CO_2), the olfactory system (H_2S), or both systems (carvone). Subjects rated the intensity of each stimulus quality when presented either alone or in binary mixtures. While there were no intensity differences between the three stimuli presented alone, an interesting pattern was found among the binary mixtures (Fig. 2). The intensity of the pure olfactory stimulus, H_2S, was suppressed in mixtures with both the trigeminal stimulant CO_2 and more strongly by the mixed stimulus carvone. In contrast, when CO_2 was mixed with carvone the intensity of CO_2 was suppressed, while that of carvone was actually enhanced in the same mixture. These results reflect not only a "dominance" of trigeminal sensation over olfactory sensation, as reported previously, but also a dominance of mixed stimulation over either system alone. The authors suggested that this might reflect a superior memory trace for the mixed stimulus, which is encoded into both systems, giving more pathways for retrieval and reducing the possibility of interference. However, the results could also reflect patterns of neural suppression that have been shown to occur at both the periphery or in the olfactory bulb (see below).

Thus, the interaction between the olfactory and trigeminal systems is not straightforward, and may be difficult to predict, but has a powerful influence on odor perception both at different concentrations of a single stimulus and between different chemosensory stimuli. This pattern of interaction depends on stimulus quality, stimulus intensity and the relative intensity of olfactory and trigeminal components.

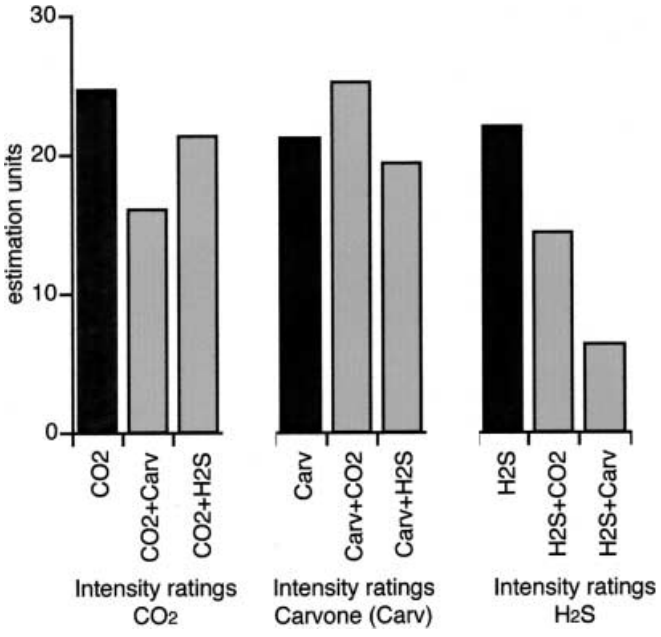

Fig. 2. Intensity ratings (means, $n=30$) in response to the individual stimuli CO_2, H_2S, or carvone (*carv*), and their binary mixtures. The intensity of H_2S was suppressed in mixtures with both CO_2 and carvone. In contrast, when CO_2 was mixed with carvone the intensity of CO_2 was suppressed, while that of carvone was enhanced (data from [83])

Sites of interaction between trigeminal and olfactory activation

At least four possible mechanisms have been identified by which trigeminal activity may influence olfactory processing (for review see [97]). Firstly, the systems interact centrally. For example, blocking of the trigeminal system facilitates odor-evoked activity in the mediodorsal thalamus of the rat [62].

Secondly, the trigeminal system may modulate the activity of the olfactory bulb both in the presence and absence of odor stimulation. Blocking of the nerve at the gasserian ganglion with lidocaine decreased background activity in the rabbit's olfactory bulb and increased the signal-to-noise ratio of odor-evoked responses [106, 107].

Thirdly, electrophysiological studies indicate that olfactory receptor responses to chemical stimuli can be modified through the release of substance P (SP) and possibly other peptides [47, 81, 93] from trigeminal fibers innervating the olfactory epithelium [32, 77]. Application of SP to the olfactory epithelium induces transepithelial and single-cell responses that resemble odor-evoked activity, that is, an increase in excitation [10, 11, 35]. Furthermore, electrical stimulation of the ophthalmic branch of the frog equivalent of the trigeminal nerve (NV-ob) resulted in increased spontaneous receptor firing, modified mass neuronal activity in the mucosa, and reduced amplitude of both the electro-olfactogram and single unit responses to the odorant isoamyl acetate. Topical application of SP was also found to modify receptor responses to the odorant [11].

Lastly, trigeminal activation may influence olfactory perception indirectly via nasal trigeminal reflexes designed to minimize potentially damaging exposure to noxious substances. This can occur, for example, by alteration of nasal patency and respiration, or changing the constitution and consistency of the mucus layer covering the epithelium as a result of stimulation of glands and secretory cells [32]. Therefore, in addition to direct alteration of receptor cell activity, the release of peptides from trigeminal fibers in the epithelium may influence receptor responses to odorants by changing the physical conditions in the receptor environment.

Consequences of olfactory loss

There are few reports on olfactory modulation of trigeminally mediated sensations. Walker and Jennings [114] reported an increase of nasal irritation thresholds for acetic acid, propionic acid, and amyl acetate in anosmic subjects. Similar findings had already been obtained in experimental animals [46, 115]. Research also indicates that olfactory activation increases sensitivity to trigeminally mediated stimuli [71, 83]. This has

been shown on an electrophysiological level where patients with anosmia exhibit smaller responses to trigeminal ERPs [49]. On a behavioral level, respiratory reflexes to intranasal trigeminal stimuli are found to be significantly faster and stronger in normosmic individuals than in anosmic subjects [66]. Psychophysical measures of trigeminal function also indicated decreased sensitivity in anosmic patients [38, 116]. And finally, clinical observations [72, 112] indicate that olfactory loss is frequently accompanied by a decreased responsiveness to trigeminal stimulation. However, these changes of trigeminal sensitivity in relation to olfactory activation are still a matter of debate, as other studies suggest that olfactory dysfunction has little effect on trigeminal sensitivity (e.g., [23]). For example, zinc sulfate ($ZnSO_4$)-induced anosmia in mice had no influence on irritation-induced respiration changes [42].

Conclusions

In this review we have attempted to outline characteristics of the intranasal trigeminal chemosensory system. In addition, we have selectively compared and contrasted the trigeminal with the olfactory system, the two of which interact at multiple levels. This interaction is an important determinant of odorous sensations. Further, it changes as a result of aging and disease. Thus, the interaction between the olfactory and trigeminal systems is not straightforward and may be difficult to predict, but it has a powerful influence on the perception of odors.

References

1. Adriaensen H, Gybels J, Handwerker HO, Van Hees J (1983) Response properties of thin myelinated (A-delta) fibers in human skin nerves. J Neurophysiol 49:111–122
2. Alimohammadi H, Silver WL (2000) Evidence for nicotinic acetylcholine receptors on nasal trigeminal nerve endings of the rat. Chem Senses 25:61–66
3. Anton F, Peppel P (1991) Central projections of trigeminal primary afferents innervating the nasal mucosa: a horseradish peroxidase study in the rat. Neuroscience 41:617–628
4. Anton F, Peppel P, Euchner I, Handwerker HO (1991) Controlled noxious chemical stimulation: responses of rat trigeminal brainstem neurones to CO_2 pulses applied to the nasal mucosa. Neurosci Lett 123:208–211
5. Anton F, Euchner I, Handwerker HO (1992) Psychophysical examination of pain induced by defined CO_2 pulses applied to the nasal mucosa. Pain 49:53–60
6. Barnett EM, Evans GD, Sun N, Perlman S, Cassell MD (1995) Anterograde tracing of trigeminal afferent pathways from the murine tooth pulp to cortex using herpes simplex virus type I. J Neuroscience 15:2972–2984
7. Bernard JF, Peschanski M, Besson JM (1989) A possible spino (trigemino)-ponto-amygdaloid pathway for pain. Neurosci Lett 100:83–88
8. Bevan S, Yeats J (1991) Protons activate a cation conductance in a subpopulation of rat dorsal root ganglion neurones. J Physiol 433:145–161
9. Bevan S, Forbes CA, Winter J (1993) Protons and capsaicin activate the same ion channels in rat isolated ganglion neurones. J Physiol 459:401P
10. Bouvet JF, Delaleu JC, Holley A (1987) Olfactory receptor cell function is affected by trigeminal nerve activity. Neurosci Lett 77:181–186
11. Bouvet JF, Delaleu JC, Holley A (1988) The activity of olfactory receptor cells is affected by acetylcholine and substance P. Neurosci Res 5:214–223
12. Cain WS (1976) Olfaction and the common chemical sense: some psychophysical contrasts. Sens Process 1:57–67
13. Cain WS (1977) Bilateral interaction in olfaction. Nature 268:50–53
14. Cain WS (1982) Odor identification by males and females: prediction vs. performance. Chem Senses 7:129–142
15. Cain WS, Murphy C (1980) Interaction between chemoreceptive modalities of odor and irritation. Nature 284:255–257
16. Caterina MJ, Julius D (1999) Sense and specificity: a molecular identity for nociceptors. Curr Opin Neurobiol 9:525–930
17. Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR, Koltzenburg M, Basbaum AI, Julius D (2000) Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science 288:306–313
18. Chakour MC, Gibson SJ, Bradbeer M, Helme RD (1996) The effect of age on A delta- and C-fibre thermal pain perception. Pain 64:143–152
19. Chen X, Belmonte C, Rang HP (1997) Capsaicin and carbon dioxide act by distinct mechanisms on sensory nerve terminals in the cat cornea. Pain 70:23–29
20. Chudler EH, Dong WK, Kawakami Y (1985) Tooth pulp evoked potentials in the monkey: cortical surface and intracortical distribution. Pain 22:221–223
21. Cometto-Muñiz E, Cain WS (1984) Temporal integration of pungency. Chem Senses 8:315–327
22. Cometto-Muñiz JE, Cain WS, Abraham MH (1998) Nasal pungency and odor of homologous aldehydes and carboxylic acids. Exp Brain Res 118:180–188
23. Cometto-Muñiz JE, Cain WS, Abraham MH, Kumarsingh R (1998) Sensory properties of selected terpenes. Thresholds for odor, nasal pungency, nasal localization, and eye irritation. Ann N Y Acad Sci 855:648–651
24. Cometto-Muñiz JE, Cain WS, Hudnell HK (1997) Agonistic effects of airborne chemicals in mixtures: odor, nasal pungency, and eye irritation. Percept Psychophys 59:665–674
25. Cometto-Muñiz JE, Garcia-Medina MR, Calvino AM, Noriega G (1987) Interactions between CO_2 oral pungency and taste. Perception 16:629–640
26. Cometto-Muñiz JE, Hernandez SM (1990) Odorous and pungent attributes of mixed and unmixed odorants. Percept Psychophys 47:391–399
27. Doty RL (1995) The Smell Identification Test Administration Manual, 3rd edn. Sensonics Inc, Haddon Heights, New Jersey, USA
28. Doty RL, Bromley SM, Moberg PJ, Hummel T (1997) Laterality in human nasal chemoreception. In: Christman S (ed) Cerebral asymmetries in sensory and perceptual processing. North Holland Publishing, Amsterdam, pp 497–542
29. Doty RL, Brugger WPE, Jurs PC, Orndorff MA, Snyder PJ, Lowry LD (1978) Intranasal trigeminal stimulation from odorous volatiles: psychometric responses from anosmic and normal humans. Physiol Behav 20:175–185
30. Dunn JD, Cometto-Muñiz JE, Cain WS (1982) Nasal reflexes: reduced sensitivity to CO_2 irritation in cigarette smokers. J Appl Toxicol 2:176–178
31. Elsberg CA, Levy I, Brewer ED (1935) The sense of smell VI. The trigeminal effects of odorous substances. Bull Neurol Inst N Y 4:270–285
32. Finger TE, Getchell ML, Getchell TV, Kinnamon JC (1990) Affector and effector functions of peptidergic innervation of the nasal cavity. In: Green BG, Mason JR, Kare MR (eds) Chemical Senses: Irritation. Marcel Dekker, New York, pp 1–20
33. Fröhlich R (1851) Ueber einige Modificationen des Geruchsinnes. Akad Wiss Wien, math-nat CL 6:322–328

34. Garcia Medina MR, Cain WS (1982) Bilateral integration in the common chemical sense. Physiol Behav 29:349–353
35. Getchell ML, Bouvet JF, Finger TE, Holley A, Getchell TV (1989) Peptidergic regulation of secretory activity in the amphibian olfactory mucosa: immunohistochemistry, neural stimulation and pharmacology. Cell Tissue Res 256:381–389
36. Green BG, Lawless HT (1991) The psychophysics of somatosensory chemoreception in the nose and mouth. In: Getchell TV, R.L. D, Bartoshuk LM, Snow JBJ (eds) Smell and Taste in Health and Disease. Raven Press, New York, pp 235–253
37. Gudziol H, Gramowski KH (1987) Respirations-Olfaktometrie – eine objektivierende Methode zur quantitativen Bewertung einer Hyposmie. Laryngol Rhinol Otol 66:570–572
38. Gudziol H, Schubert M, Hummel T (2001) Decreased trigeminal sensitivity in anosmia. ORL J Otorhinolaryngol Relat Spec 63:72–75
39. Handwerker H, Kobal G (1993) Psychophysiology of experimentally induced pain. Physiol Rev 73:639–671
40. Handwerker HO, Anton F, Reeh PW (1987) Discharge patterns of afferent cutaneous nerve fibers from the rat's tail during prolonged noxious mechanical stimulation. Brain Res 65:493–504
41. Handwerker HO, Iggo A, Zimmermann M (1975) Segmental and supraspinal actions on dorsal horn neurons responding to noxious and non-noxious skin stimuli. Pain 1:147–165
42. Hansen LF, Hammer M, Petersen SH, Nielsen GD (1994) Effects of intranasal $ZnSO_4$ irrigation on olfactory and trigeminal cues. Physiol Behav 55:699–704
43. Hari R, Portin K, Kettenmann B, Jousmäki V, Kobal G (1997) Right-hemisphere preponderance of responses to painful CO_2 stimulation of the human nasal mucosa. Pain 72:145–151
44. Harkins SW, Davis MD, Bush FM, Kasberger J (1996) Suppression of first pain and slow temporal summation of second pain in relation to age. J Gerontol 51A:M260–M265
45. Harkins SW, Price DD, Katz MA (1983) Are cerebral evoked potentials reliable indices of first or second pain? In: Bonica JJ, Lindblom U, Iggo A (eds) Advances in pain research and therapy, vol 5. Raven Press, New York, pp 185–191
46. Henton WW, Smith JC, Tucker D (1969) Odor discrimination in pigeons following section of the olfactory nerves. J Comp Physiol Psychol 69:317–323
47. Holley A, Bouvet JF, Delaleu JC (1991) Evidence for interactions between trigeminal afferents and olfactory receptor cells in the amphibian olfactory mucosa. In: Green BG, Mason JR, Kare MR (eds) Chemical Senses, vol 2, Irritation. Marcel Dekker, New York, pp 61–67
48. Hoshino T, Usui N (1987) Objective olfactometry by the method of recordings of respiratory resistances. Jibiinkoka 90:516–522
49. Hummel T, Barz S, Lötsch J, Roscher S, Kettenmann B, Kobal G (1996) Loss of olfactory function leads to a decrease of trigeminal sensitivity. Chem Senses 21:75–79
50. Hummel T, Barz S, Pauli E, Kobal G (1998) Chemosensory event-related potentials change as a function of age. Electroencephalogr Clin Neurophysiol 108:208–217
51. Hummel T, Dalton P, Dilks DD (1999) Effects of exposure to irritants. Soc Neurosci Abstr 25:2187
52. Hummel T, Gruber M, Pauli E, Kobal G (1994) Event-related potentials in response to repetitive painful stimulation. Electroencephalogr Clin Neurophysiol 92:426–432
53. Hummel T, Kobal G (1999) Chemosensory event-related potentials to trigeminal stimuli change in relation to the interval between repetitive stimulation of the nasal mucosa. Eur Arch Otorhinolaryngol 256:16–21
54. Hummel T, Kraetsch H-G, Pauli E, Kobal G (1998) Responses to nasal irritation obtained from the human nasal mucosa. Rhinology 36:168–172
55. Hummel T, Livermore A, Hummel C, Kobal G (1992) Chemosensory event-related potentials in man: relation to olfactory and painful sensations elicited by nicotine. Electroencephalogr Clin Neurophysiol 84:192–195
56. Hummel T, Pauli E, Stefan H, Kettenmann B, Schüler P, Kobal G (1995) Chemosensory event-related potentials in patients with temporal lobe epilepsy. Epilepsia 36:79–85
57. Hummel T, Rothbauer C, Pauli E, Kobal G (1998) Effects of the decongestant oxymetazoline on human olfactory and intranasal trigeminal function in acute rhinitis. Eur J Clin Pharmacol 54:521–528
58. Hummel T, Schiessl C, Wendler J, Kobal G (1996) Peripheral electrophysiological responses decrease in response to repetitive painful stimulation of the human nasal mucosa. Neurosci Lett 212:37–40
59. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G (1997) "Sniffin' sticks": olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses 22:39–52
60. Hummel T, Yousem DM, Alsop DC, Geckle RJ, Doty RL (1997) Functional MRI of olfactory and intranasal chemosensory trigeminal nerve activation. Soc Neurosci Abstr 23:2076
61. Huttunen J, Kobal G, Kaukoronta E, Hari R (1986) Cortical responses to painful CO_2 stimulation of nasal mucosa: a magnetoencephalographic study in man. Electroencephalogr Clin Neurophysiol 64:347–349
62. Inokuchi A, Kimmelmann CP, Snow JB (1993) Convergence of olfactory and nasotrigeminal inputs on possible trigeminal contributions to olfactory responses in rat thalamus. Eur Arch Otorhinolaryngol 249:473–477
63. Jones-Gotman M, Zatorre RJ (1993) Odor recognition memory in humans: role of right temporal and orbitofrontal regions. Brain Cogn 22:182–198
64. Kelly JP, Dodd J (1991) Trigeminal system. In: Kandel ER, Schwartz JH, Jessell TM (eds) Principles of neural science. Elsevier, New York, pp 701–710
65. Kendall-Reed M, Walker JC (1996) Human respiratory responses to odorants. Chem Senses 21:486
66. Kendall-Reed M, Walker JC (1998) Human respiratory responses to irritants. Talk presented at the "Workshop on Sensory Irritation", 8–9 May 1998, Center for Indoor Air Research, Sea Lodge, La Jolla, California, USA
67. Kenshalo DR (1986) Somesthetic sensitivity in young and elderly humans. J Gerontol 41:732–742
68. Kettenmann B, Hummel C, Stefan H, Kobal G (1996) Magnetoencephalographical recordings: separation of cortical responses to different chemical stimulation in man. Funct Neurosci (EEG Suppl) 46:287–290
69. Kirk-Smith MD, Booth DA (1987) Chemoreception in human behaviour: an experimental analysis of the social effects of fragrances. Chem Senses 12:159–166
70. Kobal G (1981) Elektrophysiologische Untersuchungen des menschlichen Geruchssinns. Thieme, Stuttgart
71. Kobal G, Hummel C (1988) Cerebral chemosensory evoked potentials elicited by chemical stimulation of the human olfactory and respiratory nasal mucosa. Electroencephalogr Clin Neurophysiol 71:241–250
72. Kobal G, Hummel T (1988) Effects of flupirtine on the pain-related evoked potential and the spontaneous EEG. Agents Actions 23 1/2:117–119
73. Kobal G, Hummel T (1989) Brain responses to chemical stimulation of the trigeminal nerve in man. In: Green BG, Mason JR, Kare MR (eds) Chemical Senses, vol 2, Irritation. Marcel-Dekker, New York, pp 123–139
74. Koelega HS, Köster EP (1974) Some experiments on sex differences in odor perception. Ann N Y Acad Sci 237:234–246
75. Komai M, Bryant BP (1993) Acetazolamide specifically inhibits lingual trigeminal nerve responses to carbon dioxide. Brain Res 612:122–129
76. Konnerth A, Lux HD, Morad M (1987) Proton-induced transformation of calcium channels in chick dorsal root ganglion cells. J Physiol 386:603–633

77. Kratskin I, Hummel T, Hastings L, Doty R (2000) 3-Methylindole alters both olfactory and trigeminal nasal mucosal potentials in rats. Neuroreport 11:2195–2197
78. Laing DG, Willcox ME (1987) An investigation of the mechanisms of odor suppression using physical and dichorhinic mixtures. Behav Brain Res 26:79–87
79. Lang J (1989) Clinical anatomy of the nose, nasal cavity and paranasal sinuses. Thieme, Stuttgart
80. Laska M, Distel H, Hudson R (1997) Trigeminal perception of odorant quality in congenitally anosmic subjects. Chem Senses 22:447–456
81. Lewis T (1937) The nocifensor system of nerves and its reactions. Br Med J 431–435
82. Lingueglia E, de Weille JR, Bassilana F, Heurteaux C, Sakai H, Waldmann R, Lazdunski M (1997) A modulatory subunit of acid sensing ion channels in brain and dorsal root ganglion cells. J Biol Chem 272:29778–29783
83. Livermore A, Hummel T, Kobal G (1992) Chemosensory event-related potentials in the investigation of interactions between the olfactory and the somatosensory (trigeminal) systems. Electroencephalogr Clin Neurophysiol 83:201–210
84. Lötsch J, Marchl R, Kobal G (1997) The influence of stimulus duration on the reliability of pain ratings after nociceptive stimulation of the nasal mucosa with CO_2. Eur J Pain 1:207–213
85. Mackenzie RA, Burke D, Skuse NF, Lethlean AK (1975) Fiber function and perception during cutaneous nerve block. J Neurol Neurosurg Psychiatry 38:865–873
86. Minz AI (1968) Condition of the nervous system in old men. Z Altersforsch 21:271–277
87. Murphy C (1983) Age-related effects on the threshold, psychophysical function, and pleasantness of menthol. J Gerontol 38:217–222
88. Ochoa J, Mair WGP (1969) The normal sural nerve in man. I. Ultrastructure and numbers of fibres and cells. Acta Neuropathol (Berl) 13:197–216
89. Olsson MJ, Cain WS (1996) Lateralization of odor recognition. Chem Senses 21:650
90. Parker GH (1922) The common chemical sense. In: Parker GH (ed) Smell, taste, and allied senses in the vertebrates. Lippincott, Philadelphia, pp 102–109
91. Price DD (1972) Characteristics of second pain and flexion reflexes indicative of prolonged central summation. Exp Neurol 37:371–387
92. Price DD, Hu JW, Dubner R, Gracely R (1977) Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. Pain 3:57–68
93. Raja SN, Meyer RA, Ringkamp M, Campbell JN (1999) Peripheral neural mechanisms of nociception. In: Wall PD, Melzack R (eds) Textbook of Pain. Churchill Livingstone, Edinburgh, pp 11–57
94. Raymond SA, Thalhammer JG, Popitz-Bergez F, Strichartz GR (1990) Changes in axonal impulse conduction correlate with sensory modality in primary afferent fibers in the rat. Brain Res 526:318–321
95. Renner B, Meindorfner F, Kägler M, Thürauf N, Barocka A, Kobal G (1998) Discrimination of R- and S-nicotine by the trigeminal nerve. Chem Senses 23:302
96. Sekizawa SI, Tsubone H (1994) Nasal receptors responding to noxious chemical irritants. Resp Physiol 96:37–48
97. Silver WL (1991) Physiological factors in nasal trigeminal chemoreception. In: Green BG, Mason JR, Kare MR (eds) Chemical Senses, vol 2, Irritation. Marcel Dekker, New York, pp 21–37
98. Silver WL, Fraley LG, Finger TE (1991) The effects of neonatal capsaicin administration on trigeminal nerve chemoreceptors in the rat nasal cavity. Brain Res 561:211–216
99. Sinclair DC, Hinshaw JR (1950) A comparison of the sensory dissociation produced by procaine and by limb compression. Brain 73:480–498
100. Snow PJ, Lumb BM, Cervero F (1992) The representation of prolonged and intense, noxious somatic and visceral stimuli in the ventrolateral orbital cortex of the cat. Pain 48:89–99
101. Steen KH, Reeh PW (1993) Sustained graded pain and hyperalgesia from harmless experimental tissue acidosis in human skin. Neurosci Lett 154:113–116
102. Steen KH, Reeh PW, Anton F, Handwerker HO (1992) Protons selectively induce lasting excitation and sensitization of nociceptors in rat skin. J Neurosci 12:86–95
103. Steen KH, Wegner H, Kreysel HW, Reeh PW (1995) The pH-release of rat cutaneous nociceptors correlates with extracellular $[Na^+]$ and is increased under amiloride, in vitro. Soc Neurosci 21:648
104. Stevens JC, Cain WS (1986) Aging and the perception of nasal irritation. Physiol Behav 37:323–328
105. Stevens JC, Plantinga A, Cain WS (1982) Reduction of odor and nasal pungency associated with aging. Neurobiol Aging 3:125–132
106. Stone H (1969) Effect of ethmoidal nerve stimulation on olfactory bulbar electrical activity. In: Pfaffmann C (ed) Olfaction and taste. Rockefeller University Press, New York, pp 216–220
107. Stone H, Rebert CS (1970) Observations on trigeminal olfactory interactions. Brain Res 21:138–142
108. Tateyama T, Hummel T, Roscher S, Post H, Kobal G (1998) Relation of olfactory event-related potentials to changes in stimulus concentration. Electroencephalogr Clin Neurophysiol 108:449–455
109. Thürauf N, Ditterich W, Kobal G (1994) Different sensitivity of pain-related chemosensory potentials evoked by stimulation with CO_2, tooth pulp event-related potentials, and acoustic event-related potentials to the tranquilizer diazepam. Br J Clin Pharmacol 38:545–555
110. Thürauf N, Friedel I, Hummel C, Kobal G (1991) The mucosal potential elicited by noxious chemical stimuli: is it a peripheral nociceptive event. Neurosci Lett 128:297–300
111. Torebjörk HE, Hallin RG (1970) C-fibre units recorded from human sensory nerve fascicles in situ. Acta Soc Med Upsala 75:81–84
112. Van Toller S (1999) Assessing the impact of anosmia: review of a questionnaire's findings. Chem Senses 24:705–712
113. von Skramlik E (1926) Handbuch der Physiologie der niederen Sinne. Thieme, Leipzig
114. Walker JC, Jennings RA (1991) Comparison of odor perception in humans and animals. In: Laing DG, Doty RL, Breipohl W (eds) The human sense of smell. Springer, Berlin, pp 261–280
115. Walker JC, Tucker D, Smith JC (1979) Odor sensitivity mediated by the trigeminal nerve in the pigeon. Chem Senses Flav 4:107–116
116. Wysocki CJ, Cowart BJ, Varga E (1997) Nasal-trigeminal sensitivity in normal aging and clinical populations. Chem Senses 22:826
117. Yousem DM, Maldjian JA, Siddiqi F, Hummel T, Alsop DC, Geckle RJ, Bilker WB, Doty RL (1999) Gender effects on odor-stimulated functional magnetic resonance imaging. Brain Res 818:480–487
118. Zatorre RJ, Jones-Gotman M, Evans AC, Meyer E (1992) Functional localization and lateralization of human olfactory cortex. Nature 360:339–340