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Review

Olfactory/trigeminal interactions in nasal chemoreception

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Abstract

For a long time, studies devoted to intranasal chemoreception have separately considered the different systems which coexist in the human nasal cavity, especially the olfactory and trigeminal systems. For the former, the findings have contributed to a better understanding of transduction, perception and the treatment of odors. For the latter, data have contributed to the knowledge of somatosensory innervation into the nose, especially in relation to nociception. During the last two decades, an increasing number of studies focused on interactions occurring between both systems. Indeed, most odorant molecules have the propensity to simultaneously stimulate olfactory and trigeminal systems in the nasal cavity. The interactions between both systems appear complex and take place at peripheral, central or perceptual levels. Studies in neurobiology, electrophysiology, psychophysics or functional imaging contribute to determine how both olfactory and trigeminal systems coexist and how one system could influence the other in the treatment of sensory information. However, several structural, functional and methodological questions remain unsolved in the field of olfactory/trigeminal interactions and deserve further research.

Keywords: Olfactory system; Trigeminal system; Chemoreception; Odor; Irritation; Nasal pungency

Contents

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1. Introduction

Most odorants have the propensity to stimulate olfactory receptors (CN I) located in the upper recesses of the nasal cavity and free nerve endings of the ophthalmic and maxillary branches of the trigeminal nerve (CN V), distributed throughout the nasal mucosa and olfactory epithelium (Tucker, 1971). For a long time, studies have been focused on interactions between the trigeminal and the olfactory systems. Data dealing with peripheral, central and perceptual levels have been published which contribute to the understanding of the complex olfactory/trigeminal interactions in nasal chemoreception. However, several questions remain still unresolved and further research is required to delineate the processes implied from sniff to percept.

2. Trigeminal system

Trigeminal sensitivity has been investigated for a long time (Fröhlich, 1851). However, Parker (1912), using the inadequate term "common chemical sense", was probably the first to recognize that the sense of irritation produced by chemical stimuli was distinct from both olfaction and tasting. Subsequently, a lot of investigations have described several aspects and characteristics of chemical irritation (Green et al., 1990; Doty, 1995).

2.1. Peripheral level

The nasal cavity is innervated by the ophthalmic and maxillary branches of the trigeminal nerve (Lang, 1989). Sensations derived from the trigeminal nerve are somatosensory, i.e. touch, temperature or pain sensations and perception of atmospheric humidity (Kelly and Dodd, 1991; Proctor and Andersen, 1982). These feelings are usually named burning, stinging, itching, tickling, cooling, warming. Two major fiber systems, C-fibers (unmyelinated) and A_{delta}-fibers (myelinated), participate in the afferent chemosensitive innervation of the nasal respiratory epithelium (Anton and Peppel, 1991; Sekizawa and Tsubone, 1994). Both fibers are activated by the intracellular accumulation of protons which modify the membrane conductance (Steen et al., 1995), by increasing cation membrane conductance (Konnerth et al., 1987; Bevan and Yeats, 1991; Bevan et al., 1993) which generally exhibits slow desensitization (Steen et al., 1992).

In sensory nerve, the signal transduction mechanisms underlying perception of chemical stimuli are not fully understood. Although several receptors have been identified, this question remains widely uncovered. Thus, despite the discovery of ASIC (acid-sensing ion channel) family receptors, the mechanisms responsible for signaling acid-induced pain appear in a great part unresolved (Waldmann et al., 1997; Jones et al., 2004). In the same way, it is well known that the vanilloid (VR1) family receptors can be activated by a wide array of chemical as well as hot stimuli, e.g. capsaicin or other vanilloids, lipoxygenase products, noxious heat, protons (Szallasi and Blumberg, 1999). However, further research is needed to evaluate the role of these receptors in mediating responses to several airborne irritants. Other receptors as purin (P2X) (Spehr et al., 2004) and nicotinic family receptors, especially nicotinic acetylcholine and mecamylamine nicotinic receptors have also been described on trigeminal nerve endings (Alimohammadi and Silver, 2000; Lang et al., 2003).

C-fibers are preferentially involved in the mediation of burning sensations and A_{delta}-fibers preferentially in stinging sensations (Mackenzie et al., 1975). Moreover, it is well known that messages mediated by C-fibers and A_{delta}-fibers differ in their response to repeated stimuli (Price, 1972; Price et al., 1977). At short intervals, burning sensations increase due to a summation (central nervous summation of the successive inputs related to C-fiber afferent stimulation) whereas no such summation has been reported for stinging sensations which decrease in relation to the desensitization of A_{delta}-fibers.

2.2. Trigeminal pathways

The axons (C- and A_{delta}-fibers) project to the trigeminal sensory nucleus (that extends from the rostral spinal cord to the midbrain) and to the spinal, principal and mesencephalic trigeminal nuclei. 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 the superficial laminae of the spinal nucleus, namely the subnucleus caudalis and subnucleus interpolaris (Anton and Peppel, 1991). Trigeminal information is relayed to the amygdala from the trigeminal sensory nuclei via the lateral parabranchial complex (Bernard et al., 1989). Neurons of the spinal nucleus project to the ventral posterior medial nuclei of the thalamus; most ascending fibers cross toward the contralateral side and travel with the anterolateral system while some fibers ascend ipsilaterally (Barnett et al., 1995). Neuroanatomical trigeminal pathways are clearly illustrated in the book of Woolsey et al. (2002). It must be noted that electrophysiological data indicate that an area of increased trigeminal chemosensitivity might be located at the anterior third of the septum (Hummel et al., 1996b). The projection from the ventral posterior medial nucleus terminates in the primary somatosensory cortex (SI). Moreover, trigeminal chemosensory stimulation produces an activation of the secondary somatosensory cortex (Huttunen et al., 1986), for which either the left or the right nasal chamber stimulation produces a bilateral activation (Kettenmann et al., 1996). The results of Hari et al. (1997) indicated a right-hemispheric preponderance (second somatosensory cortex) of activation following CO_2 stimulation, independently of the side of stimulation. These results are in agreement with studies in animals which indicate that the second somatosensory cortex is involved in pain perception, whereas the representation of

trigeminal projections within the primary and secondary somatosensory cortex appears rather complex (Iannetti et al., 2003). Further cognitive processing of trigeminally mediated information may also occur in the ventral orbital cortex (Snow et al., 1992).

2.3. Temporal integration

A number of investigations have described several aspects and characteristics of chemical irritation (Green et al., 1990). Among them, one question which remains without a definitive response concerns the differential responses produced by a repetitive stimulation in relation to the inter-stimulus intervals (ISIs) and the chemical nature of the stimuli (Cain, 1990). In contrast to repeated stimulations with odors and tastes that typically show a reduction in stimulus intensity if the ISI is brief, trigeminal stimuli can produce increases in rated intensity during repeated stimulation with short ISI, a phenomenon known as sensitization. In contrast, if the ISI is long the perceived intensity markedly decreases, a phenomenon known as desensitization. Sensitization and desensitization by a chemical irritant have been principally investigated on the cutaneous receptors and the tongue. The first psychophysical evidence of such an effect in the oral cavity came from Stevens and Lawless (1987) who observed that when an irritant (capsaicin or piperine) was presented twice within a short interval, the second presentation produced a more intense sensation than the first. Subsequently, Green and Gelhard (1989) showed that when moderate concentrations of NaCl were presented at 1 min intervals, the sensations induced by salt increased regularly over a 15 min period. The authors noted the similarity between these sequential effects and the phenomenon of sensitization that occurs when polymodal nociceptors are subjected to intense thermal stimulation or to a chemical irritant. However, with another irritant such as ethanol (Laska et al., 1997; Trevisani et al., 2002) the sensitization process does not occur. Ethanol produces a nearly constant sensation of irritation following successive stimulations whereas the irritation generated by an ethanol stimulus was greatly increased following a NaCl stimulus. The cross-sensitization between NaCl and ethanol suggests that the two chemicals stimulate many of the same sensory fibers (Green, 1990). Contrasting the effect of chemical sensitization occurs chemical desensitization. This phenomenon was reported in the oral cavity with capsaicin when a subsequent stimulus was delivered after the initial presentation (Green, 1989). The interval between conditioning and test stimulus had to be longer than 2.5 min but no longer than 5 min for desensitization to begin to occur.

Few studies have dealt with the question of sensitization/desensitization by chemical irritants in the nasal cavity, but it would appear that the publications over the last few years have been trying to overcome this (Hummel, 2000). In the nasal cavity, the most frequent molecule used in the field of sensitization/desensitization is capsaicin (Prescott, 1999), the pungent ingredient of red peppers. In humans, psychophysical studies with capsaicin have shown sensitization when a second stimulation was delivered shortly after (less than 1 min) the first stimulation. On the contrary, when the second stimulation was delivered more than 3 or 4 min later, it produced desensitization (Sicuteri et al., 1989). Moreover, cross-sensitization or cross-desensitization between chemical irritants can occur such as demonstrated with desensitization by capsaicin which decreased the irritation provoked by citric acid in the human nasal cavity (Geppetti et al., 1993). Some pungent substances eliciting the same activation as capsaicin have been identified, and one of them could be mustard oil. Like capsaicin, mustard oil (allyl isothiocyanate) is widely used as a flavoring agent in a variety of foods in numerous countries. Allyl isothiocyanate can be prepared from the seeds of mustard plants, *Brassica nigra* or *Brassica juncea* and synthetic allyl isothiocyanate has been commercially produced since 1937. Allyl isothiocyanate applied on the skin has led to a clear burning sensation (Magerl et al., 1990), and has been found to activate all cutaneous receptors and to predominantly excite C-fiber afferents in the upper skin layers (Handwerker et al., 1991). In this field, different irritant stimuli were used to delineate the role of molecular receptors and different cellular mechanisms linked to sensitization and desensitization in relation to ISI. Mustard oil vapor delivered to the nasal epithelium elicits a burning sensation that exhibits desensitization when applied again at long ISI of 3–4 min (Brand and Jacquot, 2002). In contrast, a new application of mustard oil vapor to the nasal mucosa at a short ISI (<2 min) elicited increased irritancy ratings. In contrast, it has been recently shown (Jacquot et al., 2005) that repeated nasal stimulations with acetic acid triggering a clear stinging sensation, induced a self-desensitization whatever the ISI. Moreover, this work showed a cross-desensitization of allyl isothiocyanate by previous acetic acid stimulation whereas a previous stimulation with allyl isothiocyanate had no effect on the following response to acetic acid.

Although the nasal trigeminal sensitization and desensitization processes appear obviously depending on the pungent substances used, the molecular mechanisms involved remains unclear.

2.4. Issues and perspectives

From a peripheral point of view, the questions linked to trigeminal nerve endings receptors appear not fully resolved, especially the number of receptor types and signal transduction mechanisms. Moreover, several molecules probably activate simultaneously different receptors and little is known about the activation of trigeminal nerve endings in relation to the concentration levels. In order to progress, it could be relevant to compare the nasal cavity innervation with other structures including nerve endings in oral mucosa, cornea or skin dermis. In the same way, it must be considered that functionally different areas can be

distinguished within the nasal cavity and probably responsiveness to trigeminal stimuli depends on the site of stimulation as recently observed (Frasnelli et al., 2004). In the field of olfactory/trigeminal interactions, one of the most important question concerns the temporal integration in nasal irritation. CO_2 is frequently used as an exclusive trigeminal stimulus without olfactory activation; further research comparing molecules with a different level of trigeminal activation and preferentially activating C- or A_{delta}-fibers could be very informative in this respect.

3. Olfactory system

3.1. Peripheral level

Olfactory neurons are located in the upper recesses of the nasal ceiling. Mammals have tens of millions of olfactory receptor neurons (Hildebrand and Shepherd, 1997; Kandel et al., 2000). Cell bodies, dendrites and initial axon segments are located within the olfactory epithelium. Each olfactory neuron carries on its surface several cilia. Buck and Axel (1991) have shown that olfactory neurons via their cilia recognize and bind odorant molecules sending signals to the brain. The olfactory receptors are integral membrane proteins that belong to a superfamily of G-protein-coupled receptors. The activation of G-protein stimulates the formation of cyclic AMP and ion channels opening. The activated olfactory receptor cell elicits a signal running to the olfactory bulb in the brain. The unmyelinated axons of the olfactory receptors cells rally into bundles of approximately 200 units which cross the foramina of the cribiform plate. The axons project directly to the ipsilateral olfactory bulb in distinct areas named glomeruli. From these glomeruli located in the olfactory bulb, information is relayed further toward other parts of the brain.

3.2. Olfactory pathways

Among all senses, olfaction is unique in that second-order neurons send information directly, with primarily ipsilateral projections from olfactory bulb to primary olfactory cortex. There are only a few contralateral connections between the two hemispheres. In humans, it is well known that the olfactory bulb is connected to the primary olfactory cortex by the fibers of the lateral olfactory tract. The olfactory cortex comprises the olfactory tubercle, the anterior olfactory nucleus, the prepiriform cortex, the amygdaloid nuclei, the periamygdaloid cortex and the lateral entorhinal cortex. The major subcortical projection of the piriform cortex is the thalamus. The lateral entorhinal cortex is the major source of afferent input to the hippocampus and the amygdala (anterior/posterior nuclei) is the major source of afferent input to the hypothalamus. The piriform cortex has direct connections with a wide expanse of the orbitofrontal cortex, concurrently with the long pathway using the thalamus (mediodorsal/medioventral nuclei). The olfactory area in orbitofrontal cortex corresponds largely to the Brodmann area 11.

3.3. Issues and perspectives

In the olfactory system, receptors signal transduction and pathways are well known today. The major questions focused now on perception and treatment of olfactory information by the central nervous system. As the link between olfaction and emotion has been largely explored, the current questions concern rather the link between olfaction and cognition. More largely, the specificity of olfactory memory, the influence of odors on cognitive processes as learning or attention seems to be the most relevant. Finally, in the perspective of olfactory/trigeminal interactions, the effect of odors on behavior raises questions on the arousal activation (at short and long time) and delineates the role of the autonomic nervous system.

4. Neurobiological interactions

As early as the nineteenth century, the philosopher Alexander Bain noted that concentrated carbon dioxide (carbonic acid) evoked pungency and remarked "if a current of carbonic acid accompanies an odor, the effect (odor) is arrested" (Bain, 1868). Later, Katz and Talbert (1930) observed that a vapor with both odor and pungency might lose odor at high concentrations, irritation masking odor. The first neurobiological study focused on olfactory and trigeminal responses has been published by Beidler and Tucker (1956). The authors recorded simultaneously electrophysiological responses of olfactory and trigeminal fibers on rabbit nasal epithelium. They noted that a trigeminal nerve response was observed with most odors that stimulated olfactory receptors.

As previously noted, sensations resulting from CN I stimulation are those of odors (e.g. the smell of flowers or grass). In contrast, sensations from stimulation of CN V are somato-sensory, and include tactile sensations, burning, cooling, tickling, pungency, warming, and the perception of atmospheric humidity. Fibers of the trigeminal nerve have been shown to innervate the olfactory epithelium (Finger et al., 1990) and several studies indicate that olfactory receptor responses to chemical stimuli can be modified by activation of the trigeminal nerve. Electrophysiological studies suggested that trigeminal stimuli have an inhibitory effect on olfactory afferents to the brain (Bouvet et al., 1987a; Kobal and Hummel, 1988). Inversely, single neuronal responses following odorant stimulation in rats are enhanced when the trigeminal afferent activity is blocked by a local anesthetic (Inokuchi et al., 1993). Probably, such changes result from both central (Stone et al., 1968; Stone, 1969; Stone and Rebert, 1970) and peripheral (Bouvet et al., 1987a, b, 1988) interactions. The latter interactions may take place via an axonal reflex

(Finger et al., 1990). Olfactory–trigeminal interactions may take place in the mediodorsal nucleus of the thalamus where convergence between olfactory and trigeminal afferents occurs.

A large variety of odorants differentially stimulate both the olfactory and the trigeminal system (Doty et al., 1978). For example, odorants frequently used as n-butanol and pyridine have stronger trigeminal components than do more purely olfactory stimuli such as phenyl ethyl alcohol (rose-like odorant) or vanillin. CN I and CN V differ with regard to their central projections and the degree to which their pathways project both contralaterally and ipsilaterally (Doty et al., 1997). The olfactory system sends information directly by primarily ipsilateral projections and there are only some contralateral afferent and efferent connections between both sides (via the anterior commissure, the corpus callosum and probably the hippocampal commissure). Most ascending fibers of the trigeminal system cross to the contralateral side while only some fibers ascend ipsilaterally.

Many investigations have described several aspects and characteristics of chemical irritation (Hummel, 2000; Sekizawa and Tsubone, 1994) and could explain the possible mechanisms by which trigeminal activity may influence olfactory processing (Silver, 1991). As previously noted, in the field of the intranasal trigeminal chemosensory modality, the most frequent molecule used is capsaicin. This chemical irritant is known to activate the chemosensitive C-fibers afferents and to induce a local and central release of substance P (SP) and other neuropeptides (Holzer, 1991). Electrophysiological studies indicated that spontaneous activity of olfactory receptors cells can be modified via a local axon reflex triggered by odors and inducing the release of SP with the concomitant analgesic effect, and other peptides (Bouvet et al., 1988) from trigeminal fibers innervating the olfactory epithelium (Kratskin et al., 2000). This modulation capacity of olfactory receptor responses to chemical stimuli could be related to the decrease of olfactory sensitivity obtained after trigeminal activation. Otherwise, it has been shown that an application of capsaicin could induce an increased nasal vascular permeability (Kitajiri et al., 1993). Thus, trigeminal activation may indirectly influence olfactory perception. 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 (Hummel and Livermore, 2002).

Otherwise, results of a recent study raised the possibility that the trigeminal and olfactory systems could also interact at central level (Schaefer et al., 2002). These recent findings showed that some trigeminal ganglion cells with sensory endings in the nasal epithelium send branches reaching directly both the spinal trigeminal complex and the olfactory bulb. Thus, the collateral innervation of the epithelium and bulb may provide a way whereby nasal irritants could affect processing of olfactory treatment.

Neurobiological interactions between olfactory and trigeminal system remain a largely opened field for further research. From a neuro-anatomical point of view, several characteristics which could have an influence on nasal chemoreception must be considered. First, two stems of the trigeminal nerve reach the nasal cavity: the ophthalmic branch innerves the region of olfactory epithelium whereas the maxillary division innerves the anterior portion of the nasal cavity. Whether a counting of free nerve endings has been realized on skin (Tschachler et al., 2004), no published study offers an equivalent counting in the nasal epithelia. Thus, density and distribution of trigeminal receptors among the nasal mucosa could play a role on olfactory interactions, especially in relation to the accessibility of odorant molecules (for instance, via ortho- or retro-nasal route). Second, as previously noted, the differential activation and repartition of C- and A_{delta}-fibers in relation to the molecules tested could be relevant as well as the parameters which currently modify the molecules properties (e.g. temperature) or the nostril functioning (e.g. the nasal cycle of congestion). Third, from a physiological point of view, very few information is available concerning the possible influence of odorant molecule on trigeminal system. Finally, little is known about central olfactory/trigeminal interactions which appear complex and strongly dependent of stimulus qualities (hedonicity, familiarity, intensity,…) and methods of stimulation.

5. Psychophysical studies

The first evidence of a difference between olfactory and trigeminal perception concerns the unilateral localization of stimulus. Indeed, it is well known that selective CN I stimulants presented to one nasal cavity cannot be localized to that cavity; however, this is not the case with CN V stimulants (von Skramlick, 1925; Kobal et al., 1989; Wysocki et al., 1992, Cometto-Muniz and Cain, 1998). The second evidence of a difference was reported in anosmic populations. Interestingly, it has been demonstrated that anosmics can detect via pungency the presence of a nasal stimulus (Doty et al., 1978; Cometto-Muniz and Cain, 1990). However, some studies reported indications for dysfunction of intranasal trigeminal sensitivity in patients with olfactory loss (Van Toller, 1999; Gudziol et al., 2001). A recent work (Hummel et al., 2003) indicated that patients with olfactory dysfunction have lower trigeminal sensitivity compared with normosmic controls, whatever the cause of olfactory loss. Additionally, the deficit appeared to improve with duration of the olfactory dysfunction, a fact which suggests possible adaptive mechanisms. Another difference concerns the perceived intensity in relation to rising concentration. Thus, the perceived intensity of a trigeminal stimulus increases much more sharply than that for the olfactory stimulus (Cain, 1976; Cometto-Muniz and Hernandez, 1990). Finally, the age-related decrease of intranasal trigeminal sensitivity appears similar to the decline of olfactory sensitivity (Stevens et al., 1982;

Murphy, 1983; Laska, 2001; Wysocki and Cowart, 2003; Frasnelli and Hummel, 2003; Shusterman et al., 2003), and sex differences in trigeminal sensitivity could occur (Frasnelli and Hummel, 2005).

The interaction between odor and pungency has been described as a reciprocal inhibition when different stimuli were used for eliciting odor and irritation (Cain and Murphy, 1980; Cometto-Muniz and Hernandez, 1990), showing that it may be an important determinant of odorous sensations. In the experiment of Cain and Murphy, 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, which confirmed that pungency could diminish odor. In the same experiment, CO_2 was also presented (two seconds) before amyl butyrate (2 s on the same inhalation) in order to see whether sequential presentation of irritant before odor would alter the pattern of inhibitory response or not. It was discovered that irritation inhibited odor perception, but only by about one-fourth the amount noted with simultaneous presentation. In the same manner, a recent work (Jacquot et al., 2004a) examined whether sequential presentation of irritant before odor specifically altered the sensitivity response. The results showed that whatever the odorant (phenyl ethyl alcohol a quasi-pure olfactory stimulant or butanol a mixed olfactory/trigeminal stimulant), the threshold sensitivity obtained after irritant stimulation (mustard oil) was lower than that obtained in normal condition. Thus, previous trigeminal activation induced an increase in olfactory sensitivity and it must be argued that both time and intensity of stimulations probably play a role in modulating interactions. Moreover, the concentration levels (peri-threshold or supra-threshold) appear to play a role on the detectability of mixtures (Cometto-Muniz et al., 2001, 2004). Finally, it must be considered that stimulation methods (e.g. large vessels vs small jars) and environmental conditions (e.g. temperature) seem to play an important role in nasal trigeminal detection (Cometto-Muniz et al., 2005).

For a long time, studies have dealt with the interrelationships between odors and pungency in order to assess their role in odor perception but few reports focused on olfactory modulation of trigeminally mediated sensations. It has been shown in normosmic subjects that trigeminal stimuli are perceived as more intense when they were accompanied by olfactory stimulation (Livermore et al., 1992; Roscher et al., 1997). Specifically, both hydrogen sulfide and vanillin considered as pure olfactory nerve stimulants (Doty et al., 1978; Kobal and Hummel, 1998) produced an increase of the perceived intensity of CO_2 (which selectively activate the intranasal trigeminal system without olfactory stimulation) stimuli.

In summary, psychophysical studies give some information about the differences in nasal irritant sensitivity by age, gender and pathologies, the inhibition or reinforcement of one system upon the other but those interactions are ill-informed overall. Actually, it seems necessary when hypothesizing about olfactory/interactions to explore the responses of each system independently to the other. Anosmic patients in the case of acquired or congenital anosmia offer the opportunity to explore the trigeminal sensitivity alone. Unfortunately, there are inversely few patients with normal olfactory functioning but devoid of trigeminal sensitivity. In other sensorial modalities such as taste or touch, it is well known that perception includes different afferent information but the response given by psychophysical investigation is rarely efficient in the discrimination. On the contrary, psychophysical studies seem more informative in two largely unexplored fields. The first concerns the temporal integration of bimodal odors related to the ISI and their concentration. The second concerns the intranasal effects in the case of long-term exposure to inhaled chemicals. Indeed, occupational and indoor exposures to chemicals are frequently associated with complaints related to nasal chemoreception. Moreover, inhaled chemicals usually have the propensity to activate both olfactory and trigeminal systems and experimental studies in toxicology could shed light on bioresponses into the nasal cavity and concomitant perceptive modifications.

6. Electrophysiological and imaging studies

6.1. Electrophysiological investigations

For a long time, electrophysiological measures have contributed to assess olfactory/trigeminal interactions. At peripheral level, the negative mucosal potential (NMP) can be recorded from the surface of the respiratory epithelium. NMP amplitudes and intensity ratings vary according to trigeminal chemoreceptor activation (Thürauf et al., 1991). In contrast, a pure olfactory stimulus did not elicit a NMP response from the respiratory epithelium (Hummel et al., 1998). At cortical level, the event-related potentials (ERPs) have been used in the study of olfactory/trigeminal interactions (Hummel and Kobal, 1992; Hummel et al., 1992; Livermore et al., 1992). First, the data indicated that classical characteristics of olfactory and trigeminal ERPs are different. Chemosensory evoked responses to vanillin and hydrogen sulfide (two pure olfactory odorants, one pleasant, the other unpleasant) have similar distribution (Kettenmann et al., 1997) which are both different from the distribution obtained with trigeminal stimuli (Kobal and Hummel, 1988, 1990). Second, studies using ERPs or reflex responses to intranasal trigeminal stimuli (Hummel et al., 1996a; Kendall-Reed et al., 1998) confirmed the psychophysical results presented above, i.e. a loss of olfactory sensitivity resulted in a decrease of the response to trigeminal stimuli, possible sex differences (Lundström et al., 2005; Lundström and Hummel, 2006), and variability in relation to the hormonal state (Olofsson et al., 2005).

Using skin conductance response (SCR) as a measure of autonomic nervous activation, Jacquot et al. (2004b) showed that odorants with trigeminal component had the ability to produce SCRs with lower concentrations than those noted for psychophysical and self-evaluated thresholds, whereas odorant without trigeminal component induces SCRs only with higher concentrations than those noted for psychophysical and self-evaluated thresholds. These findings suggest that an autonomic activation can be recorded even though the subjects have not awareness of the nasal stimulus. As previously suspected and named unconscious odor detection (Radil and Wysocki, 2000), this fact is observed in the case of an odorant with trigeminal component only. These findings are also in agreement with another study (Van Toller et al., 1983) using androstenone, a putative human pheromone. The authors noted that subjects who presented specific anosmia to androstenone gave small SCRs without response to the blank trial, and already postulated that autonomic response to androstenone might have been due to a trigeminal stimulation.

6.2. Cerebral imaging investigations

Last decade, several olfactory studies have dealt with the cerebral imaging techniques. However, few works have been devoted to the differences in cerebral activation by olfactory and trigeminal odorants (for reviews see Zald and Pardo, 2000; Savic, 2001, 2002). The work of Yousem et al. (1997) examined healthy subjects using a 1.5 T system with echoplanar imaging under conditions of repetitive stimulation with olfactory system-mediated or olfactory and trigeminal nerve-mediated odorants. The results showed that olfactory nerve-mediated and combined olfactory and trigeminal nerve-mediated odorants activated different regions in the brain. Orbitofrontal stimulation spread to every part of the brain when a trigeminal component was added. Finally, trigeminal stimulating odors have been shown to produce bilateral brain activation. In a PET study (Savic et al., 2002), it has been observed that the pattern of cerebral activation during processing of the strongly trigeminal odor acetone was very different from the processing of the pure olfactory odor vanillin. Acetone smelling evolved large activations in pons and mesencephalon, thalamus and hypothalamus, mid-cerebellum, bilaterally in anterior and posterior insular cortex and in the anterior cingulated and postcentral gyrus. Vanillin smelling activated piriform cortex, left amygdala and left insula. The authors suggest that acetone's limited activation of the olfactory cortex may result from an inhibition of acetone's odor component by its trigeminal component.

The assumption of a differential hemispheric asymmetry in relation to the quality of nasal input (olfactory/trigeminal) is in agreement with the findings of recent research using new cerebral imaging techniques (for reviews see Brand, 1999; Brand et al., 2001) in accordance with other investigation techniques (Brand and Jacquot, 2001; Brand et al., 2002). For instance, in the previous cited work of Savic et al. (2002), acetone activated only a minor part of amygdala and piriform cortex selectively on the right-hand side, whereas vanillin activated clearly these regions on both sides of the brain. Similarly, gender effect has been poorly explored in terms of olfactory/trigeminal activation. Using pure and mixed olfactory/trigeminal stimuli, a study (Bengtsson et al., 2001) compared cerebral activation with PET scans in male and female populations. No gender difference was detected in the pattern of cerebral activation in relation to the nature of stimulus. These findings are in accordance with previous brain imaging studies investigating sex-linked differences (Levy et al., 1997; Yousem et al., 1999).

6.3. Issues and perspectives

Electrophysiological and imaging studies are undoubtedly the most promising approaches for a better understanding of olfactory/trigeminal interactions. Indeed, the majority of questions raised above could be investigated with these methods from the sensorial quality of nasal stimulus (olfactory vs trigeminal) to temporal integration (sensitization vs desensitization) from concentration of nasal stimulus (low irritation vs pain) to long-term exposure effects, from inter-individual differences (by age, sex, hormonal state, etc.) to specific pathologies (anosmics, etc.). Finally, electrophysiological and imaging studies are complementary approaches insofar as the former appears as more functional and the second as more structural. Coupled with autonomic activation recordings, it could constitute an integrative investigation for resolving the complex question of olfactory/trigeminal interactions.

7. Conclusions

The nasal chemoreception which frequently implies both systems (olfactory and trigeminal) reveals specificities in the field of sensory perception. Indeed, each system presents proper characteristics in terms of localization, transduction, pathways, central projections, emotional and cognitive treatment. Moreover, the intranasal trigeminal system mediates a relatively limited spectrum of sensations as compared to the large number of different odors mediated by the olfactory system. Finally, the trigeminal system is more implied in protective reflexes than the olfactory system which is specially implied in identification, recognition, memory and fundamental behaviors of mankind. In spite of these structural and functional differences, both olfactory and trigeminal systems are simultaneously activated by the same stimuli in the nasal cavity (except few molecules which selectively stimulate either intranasal chemical sense) connected to a global perception.

The relevant question about the interactions between both systems (olfactory and trigeminal) how they coexist and how one system could influence the other in the

treatment of information appears not clearly determined today. This uncertainty could be due to the fact that only few studies focused specifically on these interactions and it could be argued that several studies focused on olfaction were inaccurately interpreted as they used odors which involved at the same time the trigeminal system. This topic appears extremely vast because mutual interactions exist at peripheral, central or perceptual levels and differ dependently of molecules, intensity or context of inhalation. Specifically, if interactions between the trigeminal and the olfactory system remain unclear and still unresolved, one major reason could be that both time and intensity of stimulation appear to play a possible role in modulating such interactions. Thus, it is not possible to accurately predict the perceptual response to odorants (and undoubtedly odorant mixtures) without understanding patterns of facilitation or suppression that result from interactions between the olfactory and trigeminal systems. At least, from a methodological point of view, when choosing odorants for use in olfactory assessment, careful attention of their trigeminal properties must be given, especially in the new well-developed functional imaging studies.

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