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Trigeminal Chemesthesis

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<https://escholarship.org/uc/item/42n8h94s>

ISBN

9781118971758

Authors

Cometto-Muniz, J. Enrique
Simons, Christopher

Publication Date

2015

Data Availability

The data associated with this publication are within the manuscript.

Peer reviewed

Trigeminal Chemesthesis. In: Handbook of Olfaction and Gustation, 3rd Edition. Chapter 50, Wiley-Blackwell: Hoboken, New Jersey, 2015, pp. 1091-1112.

Chapter 50: Trigeminal Chemesthesis

J. Enrique Cometto-Muñiz^{1*} and Christopher Simons²

¹Chemosensory Perception Laboratory, University of California, San Diego, California, USA

²Department of Food Science and Technology, The Ohio State University, Columbus, Ohio, USA

* Correspondence to Dr. J. Enrique Cometto-Muñiz at: ecometto@ucsd.edu

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1) Introduction

In addition to the classical modalities of smell (olfaction) and taste (gustation), all body mucosae can respond directly to chemicals in our environment. This broadly distributed mucosal chemosensitivity was originally labeled the “common chemical sense” (Parker, 1912). In fact, such chemical sensitivity is also present in the skin, under the epidermis (Keele, 1962). The name remained until not long ago (Cain, 1981; Silver, 1987) and it is still occasionally used. More recently, this chemosensory modality is referred to as “chemesthesis” or “chemesthesia”, in analogy to “somesthesis”, since one can think of it as “chemically-induced somesthesis” (Green and Lawless, 1991; Green et al., 1990b). In simpler words, chemesthesis conveys the concept of chemical “feel” for sensations that are neither odors nor tastes (Bryant and Silver, 2000; Green et al., 1990a). Mucosal chemesthetic sensations are usually sharp and/or pungent. They include: prickling, piquancy, stinging, irritation, tingling, freshness, coolness, burning, and the like.

Although, as mentioned, all body mucosae possess chemosensitivity, those most exposed to environmental chemicals are the face mucosae: nasal, ocular, and oral. Early studies already had established that the trigeminal nerve (cranial nerve V, CN V), which provides chemical sensitivity to these three mucosae, is responsible for a variety of physiological responses to chemical irritants (Allen, 1928; 1929a; b; Dawson, 1962; Stone et al., 1966; Stone and Rebert, 1970; Stone et al., 1968; Ulrich et al., 1972). Thus, it is quite appropriate that this chemosensory system is now often referred to as “trigeminal chemoreception” (Cometto-Muñiz et al., 2010; Doty and Cometto-Muñiz, 2003; Doty et al., 2004; Silver and Finger, 2009; Silver and Finger, 1991). Previous reviews have described in detail the anatomy and physiology of the trigeminal

chemosensory system (Doty and Cometto-Muñiz, 2003; Doty et al., 2004). Briefly, the three branches of the trigeminal nerve -- the ophthalmic, the maxillary, and the mandibular -- provide the bulk of chemesthetic sensitivity to the ocular, nasal, and oral mucosae. The glossopharyngeal (CN IX) and vagus (CN X) nerves also contribute to chemesthesis in the mouth (posterior tongue) and the nasopharyngeal and pharyngeal (throat) areas. Studies in mice and rats have shown that nasal solitary chemoreceptor cells (SCCs) can contribute to nasal chemesthesis (Finger et al., 2003; Silver and Finger, 2009; Tizzano et al., 2010), although their development and survival does not seem to be dependent on intact trigeminal innervation (Gulbransen et al., 2008a). SCCs express receptor proteins involved in gustatory chemoreception (T1Rs, T2Rs) and, thus, are also related to the sense of taste (Gulbransen et al., 2008b; Ohmoto et al., 2008; Sbarbati et al., 2004; Tizzano et al., 2011). However, expression of these receptors is thought to enable identification of potentially noxious irritants or pathogenic secretions (Tizzano et al., 2010). SCCs, which have also been described in several organs from the digestive and respiratory systems, have been proposed to be part of a diffuse chemosensory system (Osculati et al., 2007; Sbarbati et al., 2010).

In the present chapter we will summarize some important functional properties of the human trigeminal chemosensory system in the nasal, ocular and oral mucosae. Among others, we will address issues related to candidate molecular receptors for trigeminal chemesthesis, chemesthetic sensitivity (i.e., detection thresholds), structure-activity relationships, detection of chemical mixtures, and temporal properties of trigeminal chemesthetic sensations.

2) Molecular Receptors for Trigeminal Chemesthesis

Chemesthetic sensitivity in the mucosae of the human face (nasal, ocular, and oral) is mediated by C and A_{delta} fibers primarily from the trigeminal nerve, although in the case of oral chemesthesis, the glossopharyngeal and vagus nerves also contribute (see reviews in Doty and Cometto-Muñiz, 2003; Doty et al., 2004; Rentmeister-Bryant and Green, 1997). The ion-channels and receptors involved are expressed by a class of peripheral neurons called polymodal nociceptors since they can respond to chemical, thermal, and mechanical stimuli (Belmonte et al., 2004). Some of the channels and receptors found in trigeminal and other sensory neurons are particularly sensitive to one or another prototypical irritant. This is the case, for example, for nicotine (Alimohammadi and Silver, 2000; Thuerauf et al., 2006), capsaicin (Tominaga and Tominaga, 2005), and menthol (Xing et al., 2006). Nevertheless, the ion-channels responding to the last two chemicals are also thermoreceptors that respond to warm/hot and cool/cold temperatures, respectively. In fact, the capsaicin channel not only responds to chemically-related vanilloids (Szallasi and Blumberg, 1999), but also to unrelated VOCs (Silver et al., 2006; Trevisani et al., 2002), to other pungent compounds (Macpherson et al., 2005; McNamara et al., 2005) and even to inorganic volatiles (Trevisani et al., 2005). It has also been shown that menthol (Macpherson et al., 2006) and other pungent substances (Bautista et al., 2005; Jordt et al., 2004) interact with more than one type of channel. Even the nicotinic receptor is modulated by VOCs such as homologous alcohols (Godden et al., 2001). In turn, VOCs can stimulate trigeminal neurons that are insensitive to cooling and capsaicin, suggesting that they can activate other mechanism(s) and receptors (Inoue and Bryant, 2005). VOCs that are reactive towards tissue can produce nociception indirectly by damaging cells and producing the release of intracellular mediators like K⁺, H⁺, ATP, and glutamate, among others, which, in turn, would activate nociceptors (Garle and Fry, 2003; Lee et al., 2005; Moalem et al., 2005; Vaughan et al., 2006; Wood and Docherty, 1997).

Among the large family of transient receptor potential (TRP) ion-channels that includes the capsaicin (TRPV1) and menthol (TRPM8) receptors (Appendino et al., 2008; Inoue, 2005; Kim and Baraniuk, 2007; Woodard et al., 2007), the TRPA1 nociceptor has been implicated in the chemesthetic response to environmental irritants (Bautista et al., 2006; Macpherson et al., 2007b; McNamara et al., 2007) and even to CO₂ (Wang et al., 2010), as well as to weak organic acids (Wang et al., 2011). The TRPM5 channel has also been implicated in responses to irritants (Lin et al., 2008). At least two mechanisms have been suggested for the activation of TRPA1 by ligands (Peterlin et al., 2007). Under one mechanism, compounds such as eugenol, carvacrol, and methyl salicylate would act via a classical binding pocket (Xu et al., 2006). Under a second mechanism, electrophilic ligands such as acrolein, trans-2-pentanal, and trans-cinnamaldehyde would act by a covalent modification of thiol (cysteine) and, less likely (LoPachin et al., 2008), amine groups in the ion-channel protein (Hinman et al., 2006; Macpherson et al., 2007a). A recent review has described the molecular mechanisms of such reactions (LoPachin et al., 2008). In fact, the TRPV1 nociceptor has also been found to be activated by covalent modification of cysteine residues (Salazar et al., 2008). These studies explored the molecular/cellular and animal behavioral aspects of chemesthesis. The general picture emerging from them reflects a complex interplay of many factors and variables (acidity, temperature, release of endogenous mediators) modulating the response of any single TRP channel. Added to this is the generally broad chemical spectrum of ligands and modulators acting on any given receptor. As the chemesthetic neural message travels towards higher levels of the nervous system, convergence of input from different TRP channels (Zanotto et al., 2007) and other modulatory influences (Omote et al., 1998; Waters and Lumb, 2008) are likely to occur. In view of such complex array of factors, structure-activity approaches to trigeminal chemesthesis that rely on selective physicochemical properties of irritants governing

their transport from the gas phase to a receptor biophase (or area) constitute very useful tools to describe, model, and predict human irritation potency from VOCs as measured psychophysically (Abraham et al., 2010b; Abraham et al., 2010c).

3) Nasal and Ocular Chemesthesis

a) Separation of nasal trigeminal chemosensitivity from olfactory sensitivity

The great majority of airborne chemicals that we detect with our noses are able to produce both an olfactory and a trigeminal response (Cain, 1974; 1976). That is, they can elicit both an odor and a chemesthetic (i.e., pungent or irritative) sensation (Doty et al., 1978). As a rule, virtually all these volatiles are initially detected by smell and, if their vapor concentration keeps increasing, there is a level where they also begin to evoke nasal chemesthesis (Doty, 1975). This presents a challenge if one wishes to measure nasal pungency thresholds devoid of olfactory biases, for example by using force-choice procedures against blanks. In other words, for most chemicals, a force-choice response between a stimulus (irritant) and a blank (plain air) will be biased since the participant will easily detect the stimulus by its odor, and will do so at concentrations well below those necessary to barely elicit any trigeminal chemesthetic sensation (i.e., to reach the vapor's pungency threshold). To address this situation, investigators have employed two main strategies. The first is to measure nasal pungency (i.e., chemesthetic) thresholds in subjects lacking a sense of smell (called anosmics) but otherwise healthy, thus avoiding odor biases (Cometto-Muñiz and Cain, 1990). The second is to measure nasal localization (or lateralization) thresholds, rather than detection thresholds, where subjects seek to localize which nostril (left or right) received a puff of irritant vapor when the other nostril simultaneously receives a puff of plain air (Cometto-Muñiz and Cain,

1998; Wysocki et al., 1997). Findings obtained using these two strategies are discussed in the next section.

b) Nasal trigeminal chemosensitivity as reflected by nasal pungency thresholds in anosmics

Since anosmic subjects lack functional olfaction, any vapor that they can detect when presented to the nose has to be detected by means of the trigeminal system. Thus, one possibility to measure nasal pungency thresholds unbiased by odors is to measure them in anosmic participants. Early studies suggested that simple physicochemical properties might predict the chemesthetic potency of vapors (Doty, 1975; Doty et al., 1978). A number of physicochemical properties change orderly and systematically along homologous chemical series. These observations prompted a series of investigations that, using carbon chain length as a practical unit of chemical change, measured nasal pungency thresholds in anosmics and odor detection thresholds in normosmics (i.e., subjects with normal olfaction) towards selected members of homologous alcohols (Cometto-Muñiz and Cain, 1990), acetate esters (Cometto-Muñiz and Cain, 1991), 2-ketones and secondary and tertiary alcohols and acetates (Cometto-Muñiz and Cain, 1993), n-alkylbenzenes (Cometto-Muñiz and Cain, 1994), aliphatic aldehydes and carboxylic acids (Cometto-Muñiz et al., 1998a), and terpenes (Cometto-Muñiz et al., 1998b). They all employed a uniform methodology that included delivery of vapors via squeeze bottles, a two-alternative forced-choice procedure against blanks (mineral oil), an ascending concentration approach, a fixed-criterion of five correct choices in a row, and measurement of headspace vapor concentration in the bottles via gas chromatography (Cometto-Muñiz and Cain, 1990).

The outcome from these studies revealed the following (Figure 1): 1) In all cases, nasal pungency thresholds (NPTs) were higher than odor detection thresholds (ODTs) by a factor ranging from 1 to 5 orders of magnitude, depending on the chemical. In other words, trigeminal chemesthetic sensitivity was always lower than olfactory sensitivity by the factor mentioned. 2) NPTs and ODTs tend to decrease with carbon chain length within homologous series; that is, trigeminal and olfactory chemosensitivity increase with carbon chain length within the series. 3) Trigeminal chemosensitivity experiences a “cut-off” effect along homologous series, meaning that a certain homolog is reached that fails to elicit an NPT even at saturated vapor concentration for room temperature (see section “2. g) Cut-off effect...” further below). Once this cut-off homolog is reached, all larger homologs fail to evoke pungency as well.

Insert Figure 1 about here

c) Nasal trigeminal chemosensitivity and anosmia

The measurement of NPTs in anosmics as a method to assess trigeminal chemesthetic thresholds in normosmics, assumes that the absence of smell does not interfere in a significant way with nasal trigeminal chemosensitivity. The outcome of psychophysical and electrophysiological studies addressing this assumption have been mixed, as described below, but they lead to the conclusion that nasal trigeminal chemosensitivity is not largely different in normosmics and anosmics.

As noted earlier, psychophysical studies of nasal trigeminal chemesthetic sensitivity in normosmics need to control for odor biases since the great majority of chemicals evoke both odor and irritation but olfactory sensitivity is higher than nasal

trigeminal sensitivity (i.e., odor thresholds are lower than chemesthetic thresholds for any given chemical). Unfortunately, effective control for odor biases in normosmics cannot be established in suprathreshold intensity procedures (e.g., (Kendal-Reed et al., 1998), and is sometimes not included even in detection threshold measurement procedures, (e.g. (Gudziol et al., 2001). This could explain the apparent outcome in such studies of higher chemesthetic sensitivity in normosmics compared to anosmics. Nasal detection thresholds for the strong irritant chloroacetyl phenone were not significantly different between congenital anosmics and age- and gender-matched normosmics (Cui and Evans, 1997). The virtually odorless irritant carbon dioxide (CO₂), see (Cain and Murphy, 1980; Cometto-Muñiz and Cain, 1982; Dunn et al., 1982; García Medina and Cain, 1982), elicited lower intensity ratings in congenital anosmics than in normosmics (Frasnelli et al., 2007b) but, in contrast, it elicited intensity ratings no different in anosmics after upper respiratory tract infection or after head trauma than in normosmics (Frasnelli et al., 2007a). In terms of CO₂ detection thresholds, anosmics after upper respiratory tract infection and those after head trauma, but not hyposmics, had higher thresholds than normosmics (Frasnelli et al., 2006). A follow-up study found a similar outcome but also included congenital anosmics (Frasnelli et al., 2010). Unfortunately, CO₂ thresholds in these studies were obtained under a “yes-no” response approach without blanks, a method quite susceptible to criterion-based biases, rather than obtained under a more robust forced-choice procedure against blanks.

Electrophysiological studies on human nasal chemesthesia have explored peripheral responses, e.g., the negative mucosal potential (NMP) (Kobal, 1985; Thürauf et al., 1993), and central responses generated in the cortex, e.g., trigeminal event-related potentials (tERP) (Kobal and Hummel, 1988; Kobal and Hummel, 1998). Peripheral responses to CO₂ stimulation in congenital anosmics and in anosmics from

acquired etiologies showed a larger activation than in normosmics (Frasnelli et al., 2007a; b). In contrast, central responses to CO₂ stimulation in congenital anosmics showed no significant differences with those in normosmics (Frasnelli et al., 2007b), whereas anosmics from acquired etiologies (and hyposmics) showed a significantly smaller activation than normosmics (Frasnelli et al., 2007a; Hummel et al., 1996a). The specific origin for this smaller central activation in certain anosmics remains unclear: in some cases the smaller activation was observed for the peak-to-peak amplitude of the early P1N1 wave (Hummel et al., 1996a) but in other cases it was observed for the base-to-peak amplitude P2 and peak-to-peak amplitude N1P2 (Frasnelli et al., 2007a).

The conflicting results discussed above led us to conclude that any advantage in nasal trigeminal chemosensitivity that normosmics might have over anosmics, if indeed real, appears to be relatively small.

d) Nasal trigeminal chemosensitivity as reflected by nasal localization (i.e., lateralization) thresholds in normosmics and anosmics

A pioneer investigation concluded that nasal localization (i.e., lateralization) of chemical vapors entering the nose through the right or the left nostril cannot be achieved via olfactory stimulation (odor) but can only be achieved when the vapors additionally activate the nasal trigeminal nerve (chemesthesis) (von Skramlik, 1925). A later paper argued in favor of nasal localization via olfaction (von Békesy, 1964), but it is likely that the odorants presented were at concentrations that activated trigeminal chemesthesis. Further studies concluded that for short chemical vapor presentations, and with the head in a fixed position, nasal localization only occurs via trigeminal chemesthesis, not via smell (Kobal et al., 1989; Schneider and Schmidt, 1967). This finding provided the

opportunity to: 1) assess nasal trigeminal chemesthetic sensitivity directly in normosmics via nasal localization thresholds (NLTs), without olfactory interference, and under a robust forced-choice procedure, and 2) use NLTs to directly compare nasal trigeminal chemesthetic sensitivity in normosmics and anosmics, using a common method.

Some studies have measured nasal localization thresholds in normosmics and in anosmics for selected homologous n-alcohols, terpenes and cumene, employing a “squeeze-bottle” delivery system, an ascending concentration approach, and quantification of vapor concentrations using gas chromatography (Cometto-Muñiz and Cain, 1998; Cometto-Muñiz et al., 1998b). Their outcome suggested slightly lower NLTs for normosmics but the difference failed to achieve statistical significance. In fact, the three estimates of trigeminal chemesthetic sensitivity: NLTs in normosmics, NLTs in anosmics, and NPTs (as defined, always in anosmics) produced quite similar results (Figure 2). In two studies using a single concentration (neat vapor) of eucalyptol, with no chemical-analytical quantification, congenital anosmics (Frasnelli et al., 2007b) and anosmics from acquired etiologies (Frasnelli et al., 2007a) did not differ significantly from normosmics in their ability to lateralize that vapor. In contrast, a previous study had found the lateralization scores of normosmics to be significantly higher than those of subjects with olfactory dysfunction (both anosmics and hyposmics) when using the neat vapors from eucalyptol and from benzaldehyde, with no analytical quantification of either vapor (Hummel et al., 2003). Another investigation found that a high stimulus volume (21 ml) enhances the ability of subjects to localize neat vapors, compared to a low volume (11 ml) (Frasnelli et al., 2011b).

Insert Figure 2 about here

In conclusion, now in terms of nasal localization, the comparison of nasal trigeminal chemesthetic sensitivity between normosmics and anosmics has produced mixed results, again indicating that any sensitivity advantage for normosmics, if indeed real, seems relatively small.

e) Ocular trigeminal chemosensitivity as reflected by eye irritation thresholds in normosmics and anosmics

As noted, the trigeminal nerve also innervates the eyes, so vapors reaching the ocular mucosa can give rise to eye irritation, a key symptom invariably mentioned in studies of indoor air pollution (Korpi et al., 2009; Wolkoff et al., 2006; Wolkoff et al., 2003). Eye irritation thresholds (EITs) were measured in normosmics for homologous n-alcohols, acetate esters, 2-ketones, n-alkylbenzenes, for various terpenes, and for cumene, using a methodology analogous to that described above for NPTs, including vapor quantification via gas chromatography (Cometto-Muñiz and Cain, 1991; 1995; 1998; Cometto-Muñiz et al., 1998b). The overall outcome showed the following (Figure 3): 1) Both EITs and NPTs tend to decline with carbon chain length along homologous series. 2) In general, EITs are very close to NPTs for any given vapor, although in particular instances the EIT can be higher (e.g., ethanol) or lower (e.g., butyl acetate) than the NPT. 3) In some cases, the saturated vapor of a chemical fails to reach an NPT but does reach an EIT (e.g., 1-octanol, octyl acetate, and geraniol).

Insert Figure 3 about here

Measurement of EITs provided another opportunity to compare the trigeminal chemosensitivity of normosmics and anosmics. The outcome for 10 vapors tested

revealed similar EITs across the two groups of subjects (Figure 4), again indicating quite comparable trigeminal chemesthetic sensitivity between normosmics and anosmics, now in the ocular mucosa (Cometto-Muñiz and Cain, 1998; Cometto-Muñiz et al., 1998b).

Insert Figure 4 about here

f) Structure-activity relationships in nasal and ocular trigeminal chemesthesis

A key element for understanding how a chemosensory system functions is to establish the relationship between the structural and physicochemical properties of the stimulating chemicals and the elicited chemosensory responses, including sensitivity, intensity, and quality. In this section we discuss such relationships in terms of the initial step of a sensory response, namely, stimulus detection, i.e., thresholds, as an indicator of stimulus potency.

The wide chemical and structural variety of pungent (i.e., irritating) vapors suggests that, in many but not all cases, these irritants exert their effect via “selective” rather than “specific” processes. *Selective* processes rest on the physicochemical transfer of the irritant from the air into the nasal mucus or tear film, and its further transfer through successive biophases (i.e., biological compartments or environments) until reaching the receptor sites responsible for chemesthetic activity. In turn, *specific* effects are those where activity is mostly dependent on a narrowly defined key characteristic or property of the irritant stimulus that allows it to interact effectively with the receptor site. For example, to be active the chemical might need to be a strong electrophile, or to possess a restricted molecular configuration (e.g., only one of two

enantiomers is active), a certain molecular size (e.g., molecules above that size are inactive), or a particular chemical functional group (e.g., only thiols are active).

A number of studies have attempted to correlate trigeminal chemesthetic potency with a variety of structural and physicochemical properties, including: molecular weight, water solubility, molecular geometry, saturated vapor pressure, boiling point, adjusted boiling point, Ostwald solubility coefficient, other partition coefficients, and combinations of these and other parameters, experimental and/or calculated, (Doty, 1975; Doty et al., 1978; Hau et al., 1999; Muller and Greff, 1984; Nielsen et al., 1992; Nielsen et al., 1990; Roberts, 1986). As pointed out by (Abraham et al., 2010c), many of these attempts lacked a general mechanistic or chemical interpretation of the basis for the chemesthetic potency of pungent vapors. In contrast, a quantitative structure-activity relationship (QSAR) based on a solvation equation (Abraham, 1993a; b) has the advantage of including a mechanistic and chemical interpretation of the properties (or “descriptors”) selected to model and predict human trigeminal chemesthetic sensitivity towards airborne compounds (Abraham et al., 2010c). This solvation-based QSAR takes the following general form:

$$SP = c + e.E + s.S + a.A + b.B + l.L \quad \text{Equation (1)}$$

In the context of chemesthesis, SP (the dependent variable) is a sensory property reflecting chemesthetic potency of a series of irritants (i.e., solutes) towards humans, when the irritants reach, penetrate, diffuse, and trigger stimulation of the target mucosa (nasal or ocular). For example, SP is the logarithm of the reciprocal of nasal pungency thresholds, $\log (1/NPTs)$, or of eye irritation thresholds, $\log (1/EITs)$. (We used reciprocals so that the more potent is the irritant, the larger numerically is $1/NPT$ or $1/EIT$.) On the other side of the equation, **E**, **S**, **A**, **B**, and **L** are physicochemical properties or descriptors (independent variables) of the series of irritants. These

descriptors are defined as follows: **E** is the excess molar refraction of the irritant that can be determined from the refractive index of the compound; it represents the tendency of the irritant to interact with a receptor phase through π - or n-electron pairs. **S** is the dipolarity/polarizability of the irritant. **A** is the overall or effective hydrogen bond acidity of the irritant. **B** is the overall or effective hydrogen bond basicity of the irritant. **L** represents $\log L^{16}$ where L^{16} is the gas-hexadecane partition coefficient of the irritant at 298 °K, and it is a measure of the lipophilicity (i.e., lipid solubility) of the irritant. The constant c , and the coefficients e , s , a , b , and l are obtained by multiple linear regression analysis, but these are not merely fitted coefficients because they define the complementary physicochemical properties that characterize the receptor biophase with which the irritants interact. That is, they provide a physicochemical characterization of the environment or phase associated with the chemesthetic receptors. They do so in the following way: “ e ” gives the propensity of the receptor phase to interact with the irritant’s π - and n-electron pairs; “ s ” quantifies the receptor phase dipolarity/polarizability because a dipolar irritant will interact with a dipolar phase and a polarizable irritant will interact with a polarizable phase; “ a ” reflects the receptor phase basicity since an irritant that is a hydrogen-bond acid will interact with a basic phase; “ b ” reflects the receptor phase acidity since an irritant that is a hydrogen-bond base will interact with an acidic phase; and, finally, “ l ” measures the lipophilicity of the receptor phase area.

The solvation equation (1) has been applied to describe and model experimentally-measured human NPTs from up to 4 dozen volatile organic compounds (VOCs), including alcohols, acetate esters, ketones, alkylbenzenes, aldehydes, carboxylic acids, terpenes and other chemicals (Abraham et al., 1996; Abraham et al., 2001; Abraham et al., 2000; Abraham et al., 1998b; Abraham et al., 1998d; Abraham et al., 2007; Abraham et al., 2010b; Cometto-Muñiz et al., 1998a; 2005a). The solvation

equation was found to account for 90 to 95% of the variability in measured NPTs. There is a strong correlation between the measured and the calculated NPTs (Figure 5). The latest version of the equation, as applied to NPTs, reads as follows (Abraham et al., 2010c):

$$\text{Log (1/NPT)} = -7.770 + 1.543 \mathbf{S} + 3.296 \mathbf{A} + 0.876 \mathbf{B} + 0.816 \mathbf{L} \quad \text{Equation (2)}$$

$N = 47$, $R^2 = 0.901$, $SD = 0.312$, $F = 95$, $Q^2 = 0.874$, $PRESS = 5.1901$, $PSD = 0.351$

where **S**, **A**, **B**, and **L** (descriptor **E** was not significant) are as defined after equation (1); N is the number of data points (i.e., VOCs), R is the correlation coefficient, SD is the standard deviation, F is the F-statistic, Q and $PRESS$ are the leave-one-out statistics, and PSD is the predictive standard deviation.

Insert Figure 5 about here

The same solvation equation (1) has also been successfully applied to describe and model experimentally-measured human EITs and, quite interestingly, also Draize eye scores in rabbits (Abraham et al., 2009; Abraham et al., 2001; Abraham et al., 2000; Abraham et al., 2003; Abraham et al., 1998a; Abraham et al., 1998c; Abraham et al., 2010b). In fact, it was shown that the two data sets assessing ocular chemesthesis: the one on human EITs and the one on Draize scores in rabbits can be made compatible and actually be combined into one single QSAR including up to 91 compounds (Abraham et al., 2003; Abraham et al., 1998c). The equation combining the two types of measurement reads as follows (Abraham et al., 2003):

$$SP = -7.892 - 0.379 \mathbf{E} + 1.872 \mathbf{S} + 3.776 \mathbf{A} + 1.169 \mathbf{B} + 0.785 \mathbf{L} + 0.568 \mathbf{I} \quad \text{Equation (3)}$$

$N = 91$, $R^2 = 0.936$, $SD = 0.433$, $F = 204.5$

where $SP = \log (1/EIT)$ or $SP = \log (MMAS/P^\circ)$, i.e., a modified rabbit Draize score as previously defined (Abraham et al., 2003), and I is an indicator variable taking the value $I = 0$ for human data and $I = 1$ for Draize rabbit data. All other symbols are exactly as defined for equations (1) and (2).

The success of the solvation model to describe NPTs and EITs indicates that the VOCs included exert their chemesthetic effect mainly via selective, rather than specific, processes as defined at the beginning of this section. Instead, vapors that act mainly via specific processes might depart from the values predicted by the solvation equation. Typically, this departure is in the direction of being more potent than predicted, i.e., having a lower NPT or EIT than predicted. We can say that the solvation equation calculates the general chemesthetic potency of any vapor with certain physicochemical properties, but, if in addition, the vapor activates one or more receptors in a strongly specific manner, its potency will be greater than that calculated by the equation, and, in consequence, its NPT or EIT will be lower than calculated. Examples of pungent compounds acting specifically on certain receptors are capsaicin (Tominaga and Tominaga, 2005), nicotine (Alimohammadi and Silver, 2000) and acrolein (Bautista et al., 2006). However, some of them, e.g., capsaicin, have very little volatility. There are also compounds for which the solvation model predicts some level of chemesthetic potency but, when tested, fail to elicit chemesthesis. These cases were discovered when studying chemesthetic potency within homologous chemical series. The phenomenon, called the “cut-off” effect, is discussed in the next section.

- g) Cut-off effect for eliciting trigeminal chemesthesis along vapors from homologous chemical series

As illustrated in Figures 1, 2, 3, and 4, trigeminal chemesthetic thresholds tend to decrease with carbon chain length along homologous series (Cometto-Muñiz, 2001). Nevertheless, this trend often ends abruptly when a certain homolog is reached for which no threshold can be measured since even the saturated vapor of the compound at room temperature ($\approx 23^{\circ}\text{C}$) fails to elicit chemesthetic detection reliably (Cometto-Muñiz and Cain, 1991; 1994; 1998; Cometto-Muñiz et al., 1998a). We labeled this phenomenon a “cut-off” effect for the detection of trigeminal chemesthesia, in analogy with a similar effect described for anesthesia (Franks and Lieb, 1985; 1990; Horishita and Harris, 2008). In turn, we labeled the smallest homolog failing to elicit chemesthetic detection the “cut-off homolog”.

At least two possible mechanisms could explain the occurrence of the cut-off effect: 1) the saturated vapor concentration, at room temperature (23°C), of the cut-off homolog (and all ensuing homologs) falls below the necessary threshold, and 2) the cut-off homolog (and all ensuing homologs) lacks a key feature to trigger chemesthesia. We looked into these two possibilities by following three approaches: 1) calculating a predicted chemesthetic threshold via the solvation QSAR model described just above and comparing it with the saturated vapor concentration (at 23°C) of the cut-off homolog; 2) increasing the saturated vapor concentration of the cut-off homolog by heating it to 37°C and testing if this would precipitate detection; and 3) measuring complete concentration-detection functions (rather than just a threshold point) for the cut-off compound and for its immediate homologous neighbors (Cometto-Muñiz and Abraham, 2008; Cometto-Muñiz et al., 1998a; 2005a; b; Cometto-Muñiz et al., 2006; 2007a; b). The combined outcome from these approaches indicated that the cut-off effect often results from a restriction other than an insufficient vapor concentration; for example, it could result from reaching a large enough homolog that exceeds a critical molecular

dimension to be able to elicit chemesthesis (Cometto-Muñiz et al., 2010). If so, this molecular size restriction would constitute a specific effect (as defined at the beginning of the previous section) and, in consequence, it would not be predicted by the solvation model represented by equation (1).

h) Chemical mixtures and chemesthesis

An interesting functional aspect of trigeminal chemesthesis relates to the stimulation with chemical mixtures, both at threshold (i.e., detection) and suprathreshold (i.e., perceived intensity or magnitude) levels. When probing the rules by which trigeminal chemesthesis detects chemical mixtures, as compared to the detection of the individual constituents, it is important to rule out physicochemical interactions and associations among components that might occur before the mixture even reaches the receptor sites. This consideration is usually not addressed in mixture studies. A recent investigation concluded that, at concentrations near chemesthetic detection thresholds, the association between non-reactive VOCs in mixtures upon reaching their biological site of action would only amount to less than 5% of their total concentration (Abraham et al., 2010a).

In terms of threshold chemesthetic detection of chemical mixtures, an intensive study of nine individual VOCs from a number of homologous series and five of their mixtures including 3, 6, and 9-components, found various degrees of agonism (i.e., additive effects) among the constituents (Cometto-Muñiz et al., 1997). The investigation included two chemesthetic endpoints: NPTs and EITs, and an olfactory endpoint: ODTs. Chemesthetic thresholds showed a larger degree of agonism than olfactory ones, with eye irritation having stronger agonism than nasal pungency. The extent of

chemosensory agonism became larger as the number and the lipophilicity (i.e., lipid solubility) of the mixture components increased. Later studies followed a more detailed approach by focusing in binary mixtures and by measuring full concentration-detection (i.e., psychometric or detectability) functions, (see (Cometto-Muñiz et al., 2002), rather than just threshold values. As before, components of the mixtures were chosen from homologous series, allowing us to address the role of structure-activity relationships in the chemesthetic detection of binary mixtures (Cometto-Muñiz et al., 2004a; Cometto-Muñiz et al., 1999; 2001). The results were analyzed in terms of response-addition (i.e., sum of detectabilities) and of dose-addition (sum of doses within a selected psychometric function). The outcome pointed towards relative agreement between these two ways of quantifying addition, and indicated a larger degree of addition at low than at high levels of detectability (Cometto-Muñiz et al., 2004b). In these latter studies, which are based on concentration-detection functions, nasal pungency showed a larger degree of addition than eye irritation for mixtures presented at moderate and high detectability levels.

In terms of perceived intensity of chemical mixtures (i.e., suprathreshold range), a study of mixtures of the pungent odorants ammonia and formaldehyde revealed that, as the mixtures increased in concentration, the total nasal perceived intensity switched from being significantly lower to being significantly higher than the sum of the perceived intensities of its components (Cometto-Muñiz et al., 1989). A follow-up investigation confirmed that this effect was due to a gain in the relative contribution of nasal chemesthesis over olfaction as the concentration of the mixtures increased (Cometto-Muñiz and Hernández, 1990). In another study, the ocular mucosa seemed more responsive than the nasal mucosa regarding the chemesthetic intensity elicited by the complex mixture environmental tobacco smoke (Cain et al., 1987). Under a dose-

response approach, the eye irritation intensity produced by a mixture of 8 VOCs and two mixtures of 4 VOCs indicated that the components acted in a simple additive way to produce ocular irritation (Hempel-Jorgensen et al., 1999). A recent paper employed nasal lateralization scores and intensity ratings to compare 3 single chemicals (menthol, eucalyptol, and allyl isothiocyanate) and two mixtures (menthol/eucalyptol and menthol/allyl isothiocyanate) (Frasnelli et al., 2011a). Intensity ratings probably included odor plus chemesthesis (i.e., total nasal intensity), although it is not specifically stated. Individual stimuli were presented at a single liquid dilution (found to be iso-intense by a different group of experienced subjects) and the mixtures were presented at 50%, probably volume/volume (v/v), but no analytical quantification of the vapor concentrations from either single or mixed stimuli was presented. The results suggested suppression within the mixture activating a common receptor (i.e., menthol/eucalyptol) given that this mixture produced lower intensity ratings than the other mixture, and slightly lower lateralization scores than the other mixture (albeit only under a one-sided t-test since the main effect “stimulus” failed to reach significance for lateralization scores). This outcome should be taken with the caveat that many chemesthetic stimuli that are mainly known to activate a certain receptor type can also activate or inhibit other types (Macpherson et al., 2006) with more or less potency and/or efficacy (Lambert, 2004).

Real world chemical exposures often involve mixtures of at least dozens or hundreds of components (Feron et al., 2002). A number of investigations have looked into complex mixtures of VOCs to establish their ability to elicit nasal and/or ocular trigeminal chemesthesis in humans, at threshold and suprathreshold levels, among other diverse effects. Examples of such complex stimuli include: environmental tobacco smoke (Cain et al., 1987), fragranced products (Millqvist et al., 1999; Opiekun et al., 2003), indoor air (Hudnell et al., 1992; Laumbach et al., 2005; Meininghaus et al., 2003;

Otto et al., 1990), and outdoor air surrounding composting facilities (Müller et al., 2004), animal production facilities (Schiffman et al., 2000; Schiffman and Williams, 2005), and other industries (Dahlgren et al., 2003). In such studies, the typical goal was to assess the effect of the mixture (diluted or neat) on different groups of subjects (e.g., unexposed controls, exposed subjects, asthmatics, etc.). Since, in most cases, these very complex mixtures were not fully defined from a chemical standpoint, no attempts were made to relate the chemesthetic impact of the mixtures to that of the individual constituents.

i) Temporal properties of nasal and ocular chemesthesis

Since nasal and ocular trigeminal chemesthetic responses often act as a warning signal against the continued exposure to potentially deleterious airborne compounds, these sensations tend to increase with time of exposure before reaching a plateau or declining thereafter (Shusterman et al., 2006; Wise et al., 2009b). At near-threshold levels, an increase in stimulation time produces lower detection thresholds, at least within the first few seconds (≈ 4 -6 sec) of stimulation. This temporal integration of threshold nasal chemesthesis, whether measured with a trigeminally-induced reflex apnea (Dunn et al., 1982) or with the nasal localization approach, has been observed for a variety of irritants including ammonia (Cometto-Muñiz and Cain, 1984; Wise et al., 2005), CO₂ (Wise et al., 2004), ethanol (Wise et al., 2006), homologous alcohols (Wise et al., 2007), and homologous propionates (Wise et al., 2009a). Within short stimulation times (up to 6 sec), the relationship between exposure-time and concentration falls close but often is short of a perfect trade off; that is, to achieve the chemesthetic threshold, it takes somewhat more than doubling the stimulus duration to compensate for a twofold decrease in concentration.

At supra-threshold levels, the perceived intensity of nasal chemesthesis increases with stimulation time for at least the first 4 sec, as shown with ammonia (Cometto-Muñiz and Cain, 1984; Wise et al., 2005) and CO₂ (Wise et al., 2003). Under a protocol testing homologous alcohols with alternative cycles of 3 sec of chemical stimulation and 3 sec of clean air for a 1 min trial, the intensity of nasal chemesthesis showed adaptation, that is, it decreased for recurrent pulses of the alcohol vapor (Wise et al., 2010). Using fixed suprathreshold levels of CO₂ as the nasal chemesthetic stimulus, a series of studies have looked into the effect of repetitive stimulation with CO₂ at different inter-stimulus intervals (ranging from 2 to 90 sec) in subsequent ratings of pain intensity. They concluded that, for intervals ranging from 10 to 90 sec, pain ratings for repetitive CO₂ presentations were lowest after a 10-sec interval and largest after a 90-sec interval (Hummel and Kobal, 1999). For very short intervals (2 to 8 sec), pain ratings increased after 2-sec intervals but decreased after 6- and 8-sec intervals (Hummel et al., 1994; Hummel et al., 1996b). In contrast, the decrease in amplitude to repetitive CO₂ stimulations of both the peripheral negative mucosal potential (NMP) and the central chemo-somatosensory event-related potential (CSSERP) were more pronounced with the shortest inter-stimulus interval, i.e., 2 sec. (Hummel et al., 1994; Hummel et al., 1996b). Nevertheless, a more recent report found that the amplitude of chemosensory event-related potentials to repetitive CO₂ nasal stimulations increased when the inter-stimulus interval was shortened from 30 to 10 sec, concluding that the effect is due to trigeminal sensitization during repeated stimulation (Kassab et al., 2009). In another study, a lineal relationship emerged between the stimulus duration of a steady CO₂ pulse increasing from 100 to 300 msec and the amplitude of the P3 component of the trigeminal event-related potential, suggesting that the later components of this potential encode not only for stimulus concentration but also for stimulus duration (Frasnelli et al., 2003).

Other studies on the effect of exposure time on nasal chemesthesis explored much longer durations, in the range of minutes to hours, and under whole body exposures. Chamber studies testing formaldehyde at various fixed concentrations revealed that perceived irritation (nasal and ocular) increased with time during a 30-min exposure (Cain et al., 1986). In realistic daily home or occupational exposures to a chemical vapor that might be causing mild irritation, the nasal chemesthetic threshold for that chemical increases, revealing desensitization, but the effect does not appear to generalize to other irritants (Dalton et al., 2006; Smeets and Dalton, 2002; Wysocki et al., 1997). Exposures of two to three hours to mixtures of VOCs (Hudnell et al., 1992) and to the complex stimulus environmental tobacco smoke (Cain et al., 1987) revealed that the perceived intensity of chemesthesis clearly increases with time.

4) Oral Chemesthesis

a) Separation of oral trigeminal chemosensitivity from gustatory sensitivity

Typically, the detection of water soluble chemicals occurs in the oral cavity and is critical to the survival of organisms. In the case of gustation, chemosensitivity provides a mechanism by which foods can be instantaneously evaluated prior to ingestion. This ability has a profound impact on an organism's survival because, in the case of sweet sensitivity, it allows for the identification of potentially nutritious food sources, whereas for bitter and sour sensitivity, provides the ability to detect and avoid poisonous or spoiled foods (for review, see Brody et al., 2012). Although there are similarities, gustation is differentiated from oral chemesthesis in a number of important ways. Prototypical chemesthetic stimuli include many plant-based molecules such as (a) capsaicinoids (capsaicin from chili peppers (Szolcsányi and Jancsó-Gábor 1975;

Stevens and Lawless 1987; Green 1989; Caterina et al., 1997; piperine from black pepper (Stevens and Lawless 1987; Green 1996; Dessirier et al., 1999)), (b) isothiocyanates (allyl isothiocyanate from mustard oil (Simons et al., 2003; Jordt et al., 2004; Bandell et al., 2004) and allicin from garlic (Bautista et al., 2005) and (c) the alkaloid nicotine (Jansco et al., 1961; Dessirier et al., 1997; 1998), found in the nightshade family (Solanaceae) of plants. Ingestion of these compounds at low levels elicits a predominantly pungent or burning sensation from the oral mucosa (Keele 1962; Lawless and Stevens 1988; Rentmeister-Bryant and Green 1997) and vermilion border of the lips (Lawless 1984; Lawless and Stevens 1988), but have minor or no discernible taste qualities on their own (except for nicotine which has been described as bitter (Pfaffman 1959). Recently, oleocanthal from olive oil has been identified which elicits an irritant sensation sensed primarily from the pharynx (Beauchamp et al., 2005; Peyrot des Gachons et al., 2011). Other chemesthetic sensations include (a) pungency from ethanol (Green 1988; Prescott and Swain-Campbell 2000), cinnamic aldehyde (Prescott and Swain-Campbell 2000; Klein et al., 2011) and zingerone (Prescott and Stevenson 1996a; 1996b), (b) cooling from menthol (Eccles 1994; Cliff and Green 1994; 1996) and other compounds including icillin (Wei and Seid 1983), WS-12 (Sherkheli et al., 2010), WS-23 (Serkheli et al., 2010) and a recently identified high-potency synthetic compound that elicits a strong cooling sensation of long duration (Furrer et al., 2008), (c) warming from camphor (Green 1990; Moqrich 2005) and (d) tingling from alpha-hydroxy-sanshool (Bryant and Mezine 1999; Albin and Simons 2010) or spilanthol (Ley et al., 2006), unique compounds derived from the sechuan peppercorn and jambu fruit, respectively. These compounds are in contrast to gustatory stimuli that are usually detected at much higher levels (mM) and evoke specific taste sensations including sweet, sour, salty, bitter, umami and possibly fat (for review on fat taste, see Mattes 2011). Importantly, it should be noted that salts and acids, which evoke sensations of saltiness and sourness,

respectively, can elicit pungent sensations from the oral cavity (Simons et al., 1999; Dessirier et al., 2000b; 2001) when used at high concentrations. Thus, unlike many chemesthetic stimuli, acids and salts have both gustatory and irritant properties.

Chemesthetic and gustatory sensitivity are underpinned by different receptor families (for detailed discussion see Section 1) and different neuronal pathways and, in some cases, evoke different behaviors. Oral chemesthetic stimuli typically interact with one of three main families of receptors including members of the Transient Receptor Potential (TRP) family (for review, see Clapham 2003 and Talavera et al., 2008), nicotinic cholinergic receptors (nAChRs; Dessirier et al., 1998; Simons et al., 2003b; Thuermer et al., 2006), and outward-rectifying 2-pore potassium channels including KCNK3, KCNK9 and KCNK18 (Bautista et al., 2008). Most irritants interact with one of several ionotropic TRP channels including TRPA1, TRPM8, TRPV1, and TRPV2. Nicotine and sanshool, a compound that induces tingling sensations, activate the nAChRs, TRPA1 (see Talavera et al., 2009), and 2-pore potassium channels (Bautista et al., 2008). These receptors are expressed by polymodal nociceptors or, in the case of the 2-pore potassium channels, a mechanosensitive subpopulation of sensory neurons (Bautista et al., 2008; Lennertz et al., 2010; Patapoutian et al., 2009)). Ligand-receptor interaction evokes direct excitation of the neuron whose signal is conveyed centrally to the trigeminal nucleus (Sessle 1989; Carstens et al., 1998). From there, neural projections to the thalamus and, subsequently, primary somatosensory cortex, allow for higher processing of the nociceptive information (Sessle 1989). When ingested, chemesthetic stimuli evoke reflex pathways and aversive behaviors intended to minimize intake. Salivation (Ley and Simchen 2007) dilutes the irritant and behavioral responses reduce additional exposure. However, one central feature specific to oral chemesthesia is its contribution to flavor. The sensations associated with chilli peppers, wasabi, mustard and carbonation, while pungent, are often sought after, and contribute to the

flavor profile of many cuisines. Not surprisingly, therefore, the use of chemesthetic compounds has a long history in culinary use. Several hypotheses have been forwarded to explain the use of these aversive compounds by humans ranging from thrill-seeking (Rozin and Schiller 1980) to proposed health benefits. Interestingly, research has identified a range of health-related benefits of various chemesthetic stimuli including antibacterial activity (Ozçelik et al., 2011), cardiovascular protection (Peng and Li 2010), and anti-obesity effects (Hursel and Westerterp-Plantenga 2010).

These findings are in contrast to those ascribed to gustation. Identified in the early 2000's, gustatory receptors include the 7-transmembrane, g-protein coupled T1R (Nelson et al., 2001; 2002) and T2R (Adler et al., 2000; Chandrashekar et al., 2000) subfamilies, which are involved in the transduction of sweet and umami and bitter tastes, respectively (see Chapter 31). Although still unidentified in humans, it is believed that ionotropic channels transduce salty (Yarmolinsky et al., 2009) and sour (Yarmolinsky et al., 2009) sensations. Recently, in addition to texture and olfaction, fat has been proposed to have a gustatory component (Chalé-Rush et al., 2007) that involves activation of CD36 (Laugerette et al., 2005), the g-protein coupled receptors GPR40 (Matsumura et al., 2007; Cartoni et al., 2010) and GPR120 (Matsumura et al., 2007; Cartoni et al., 2010), and/or the inactivation of outward rectifying K⁺ channels (Gilbertson et al., 1997). These receptors are expressed in taste receptor cells which are derived from local epithelium (Stone et al., 1995) and innervated by primary neurons of the chorda tympani, glossopharyngeal and vagus nerves (for review, see Whitehead 1988). The central projection of these neurons is to specific gustatory centers in the brainstem, thalamus and insular cortex (Whitehead 1998). When ingested, tastant stimuli largely evoke innate stereotyped behaviors that can often be modified through learning. Sweet, umami and salt (low concentrations) stimuli elicit appetitive behaviors

whereas sour and bitter tastants evoke aversive behaviors which limit intake (for review, see Brody et al., 2012).

b) Structure-activity relationships in oral trigeminal chemesthesis

To date, the vast majority of psychophysical investigation linking oral irritancy to chemical structure-activity relationships (SAR) has been related to capsaicinoids. Several capsaicinoid compounds have been utilized to probe the human irritant response and identify the key structural attributes responsible for the pungency of this class of molecules. Capsaicin, the prototypical chemesthetic irritant, consists of an alkyl chain joined to a vanillyl moiety through an acyl amide (Figure 6a). This compound has been studied extensively and has been shown to elicit an irritant sensation in humans at

Insert Figure 6 about here

levels as low as 0.2 ppm (Szolcsányi 1990). Three critical structural features of capsaicin have been identified that impact the perceived pungency of this molecule. The vanillyl moiety is important and contributes greatly to the perceived pungency (Szolcsanyi and Jancso-Gabor, 1975). However, if the ring is opened, as in the case of undecenoyl-3-amino-propanol, pungency can still be elicited albeit at a significantly reduced potency (Szolcsanyi and Jancso-Gabor, 1975). The length of the alkyl chain also impacts pungency with perceived irritation peaking when carbon chain length reaches approximately ten carbons (Szolcsanyi and Jancso-Gabor, 1975). Finally, the presence of an acyl amide group contributes to perceived irritancy. Conversion of the acyl amide into an acyl ester significantly reduces pungency (Szolcsanyi and Jancso-Gabor, 1975).

Structure-activity relationships for other irritants have not been as extensively studied although a key structural feature of many irritants activating TRPA1 is their ability to covalently modify specific cysteine residues within the N-terminal domain of the channel (Hinman et al., 2006).

A substantial body of knowledge generated from the flavor and fragrance industry has provided important insight into the central features of cooling compounds. Using a pharmacophore hypothesis, key structural elements were identified for menthane carboxamides (Figure 6b), the most widely used and investigated family of cooling compounds (Furrer et al., 2008). The primary binding interaction between this class of compounds and TRPM8, its cognate receptor, is believed to be hydrophobic in nature and mediated via the menthane core (Furrer et al., 2008). Additionally, the affinity of menthane carboxamides can be modulated by the amidic moiety. Finally, the importance of two hydrogen bond acceptors in proximity to the compact menthane core was found to improve potency of these molecules (Watson et al., 1978, Furrer et al., 2008). However, it should be noted that other chemical cores have the capacity to evoke cooling (see, for example, Galopin et al., 2007). For instance, icillin, a compound having little structural similarity to menthol, is a potent activator of TRPM8 (McKemy et al., 2002; Chuang et al., 2004; Dhaka et al., 2007).

Finally, recent structure-activity relationships have been investigated for compounds that elicit a tingle sensation via blockade of 2-pore potassium channels. Sanshools (Figure 6c) are long-chained polyenamides and the prototypical stimulus to elicit the tingle sensation. Four key structural elements associated with sanshools have been identified which are necessary for the perceived sensation (Galopin et al., 2002). In particular, a N-isobutylcarboxamide motif is required as well as the presence of a cis-double bond in the fatty chain. Furthermore, the efficacy of these compounds can be

enhanced by the presence of a long fatty chain, saturation of the alpha-, beta-, gamma- and delta- carbons, and a hydroxyl on the N-alkyl group (Galopin et al., 2002).

c) Temporal properties of oral chemesthesis

A unique property of most oral chemesthetic irritants is their ability to elicit temporally dynamic patterns of irritation with repeated application. Psychophysical methods have been described that allow investigators to track oral irritation intensity across time (Lawless and Stevens 1988; Stevens and Lawless 1987; Green 1988; 1989; Dessirier et al., 1999, 2001; Prescott 1999; Prescott and Stevenson 1996a; 1996b). Using these techniques, several distinctive patterns (see Figure 7) have been described including sensitization, desensitization, cross-desensitization and stimulus-induced recovery (SIR). Interestingly, these same patterns of response have been observed electrophysiologically in single-unit recordings of trigeminal cells in Vc (Dessirier et al., 2000c; Sudo et al., 2002). Sensitization is described as the increase in perceived intensity of a given sensation upon repeated exposure. In the oral cavity, the

Insert Figure 7 about here

occurrence of sensitization is dependent upon the inter-stimulus intervals with which chemesthetic agents are applied (Green 1989; Green and Rentmeister-Bryant 1998; Prescott 1999). With short inter-stimulus intervals, typically on the order of three minutes or less, the perceived irritation grows until it reaches a plateau (Green 1991). Many, but not all, chemesthetic compounds elicit this pattern of irritation including the capsaicinoids capsaicin (Lawless 1984; Stevens and Lawless 1987; Green 1989; Prescott 1999) and piperine (Stevens and Lawless 1987; Green 1996; Rentmeister-

Bryant and Green, 1997), high concentrations of acids (Green 1996; Dessirier et al., 2000b) and salts (Dessirier et al., 2001), and menthol (Cliff and Green 1994; 1996). Interestingly, mustard oil (allyl isothiocyanate) was found to elicit a sensitizing pattern of irritation when delivered to the nasal cavity (Brand and Jacquot 2002) but not when delivered to the oral cavity (Simons et al., 2003a). Other irritants, including zingerone (Prescott and Stevenson 1996a; 1996b) and nicotine (Dessirier et al., 1997) do not evoke sensitization.

Several mechanisms underlying this phenomenon have been proposed (see Carstens et al., 2002) including the peripheral and central sensitization of nociceptive pathways that typically accompany inflammation (Willis 2009). Spatial recruitment has also been proposed as a mechanism underpinning sensitization (Carstens et al., 2002). In this model, irritant chemicals applied to the lingual surface activate chemosensitive neurons. With repeated application, the irritant compounds diffuse into the lingual epithelium where they encounter and excite previously unactivated neurons. The increasing number of activated nociceptors results in a progressive increase in the perceived intensity of the irritation sensation. Eventually, the rate of diffusion through the epithelium is equaled by the clearance rate of the compound. At this point, spatial recruitment cannot continue and the intensity of the perceived irritant sensation plateaus (see Figure 7).

When the repeated application of irritant chemicals occurs after a hiatus or at longer inter-stimulus intervals, typically greater than 5 min, self- or cross-desensitization occurs (Green 1991; Prescott and Stevenson 1996b; see Figure 7). Self-desensitization, like adaptation, is described as a decrease in perceived sensation intensity with repeated or continued application of a given chemesthetic compound. Cross-desensitization is the term given wherein application of one chemoirritant causes reduced sensitivity to subsequent applications of a second irritant. Cross-desensitization

is often used as evidence supporting the view that two compounds share the same receptor and/or neural mechanisms (e.g. Cliff and Green 1996; Dessirier et al., 2000a; Green 1996). To date, many of the chemorirritants tested in psychophysical protocols evoke desensitizing patterns of oral irritation including capsaicin (e.g. Green 1989; 1991; Szolcsányi 1990; Prescott 1999), piperine (Green 1996; Dessirier et al., 1999), ethanol (Prescott and Swain-Campbell 2000), acids (Dessirier et al., 2000b), salts (Dessirier et al., 2001), nicotine (Dessirier et al., 1997), allyl isothiocyanate (Simons et al., 2003a), cinnamic aldehyde (Prescott and Swain-Campbell 2000), zingerone (Prescott and Stevenson 1996a; 1996b), and menthol (Cliff and Green 1994; 1996).

Desensitization is likely due to peripheral mechanisms occurring at the receptor or neuronal level. In whole-cell patch-clamp experiments of trigeminal and dorsal root ganglion neurons, repeated application of capsaicin resulted in successively smaller inward currents (Liu and Simon 1996, 1998; Su et al., 1999; Yao and Qin 2009). This reduction could be mitigated by the removal of extra-cellular Ca^{+2} , suggesting the importance of this ion in regulating the process (Liu and Simon 1998). Interestingly, other capsaicinoids, including zingerone and olvanil, elicit cellular desensitization however, the mechanism appears to be Ca^{+2} -independent (Liu and Simon 1998). An additional mechanism contributing to desensitization could be the result of some irritants ability to inhibit voltage-sensitive Na^{+} channels as is the case for capsaicin (Su et al., 1999 and Liu et al., 2001). Clearly, this could also serve as the root cause of cross-desensitization.

An interesting aspect of lingual desensitization is that it can be overcome with subsequent, recurrent stimulation (Green 1996). This phenomenon, termed Stimulus-Induced Recovery (SIR; Figure 7), is both concentration- and inter-stimulus interval-dependent. Initiating and driving SIR to completion requires stimulus concentrations equal to or greater than the concentrations used to elicit the desensitized state. For

instance, in studies using capsaicin, a 33 μM solution could elicit SIR only when the desensitizing capsaicin concentration was 33 μM or lower, but not when a 99 μM or 330 μM solution was used (Green and Rentmeister-Bryant 1998). Additionally, like sensitization, initiation of SIR requires recurrent stimulus applications with short inter-stimulus intervals—the shorter the inter-stimulus interval, the greater the incidence and magnitude of SIR (Green and Rentmeister-Bryant 1998). Studies investigating the temporal dependence of SIR showed that an inter-stimulus interval greater than 60-sec was inefficient at reversing capsaicin desensitization (Green and Rentmeister-Bryant 1998). Although still speculative, the mechanism underlying SIR is thought to be the same as that underlying sensitization—namely, peripheral and/or central sensitization and spatial recruitment.

Many chemesthetic compounds activate multiple receptor sub-types. Additionally, the kinetics of sensitization, desensitization and adaptation for each of the sub-qualities can differ (Lawless and Stevens 1990). As a consequence, many chemesthetic compounds evoke unique and complex sensory profiles that are temporally dynamic. An excellent example of this occurs with lingual application of alkylamide compounds such as alpha-hydroxy sanshool (Figure 8). Sanshool has been shown to activate 2-pore potassium channels (Bautista et al., 2008), TRPV1 (Sugai et al., 2005; Koo et al., 2007; Menozzi-Smarrito et al., 2009; Riera et al., 2009) and TRPA1 (Koo et al., 2007; Menozzi-Smarrito et al., 2009; Riera et al., 2009). Additionally, lingual nerve recordings in rat have shown that sanshool activates low and high threshold cold-sensitive fibers as well as low threshold mechanosensitive fibers (Bryant and Mezzine 1999). As expected from the diverse receptor and neuronal types that are activated by these compounds, the psychophysical results are equally complex. Lingual application of a synthetic alkylamide elicits a sensation that is described as initially tingling and pungent but after approximately 15 minutes as cooling and numbing (Figure 8).

Insert Figure 8 about here

d) Threshold for oral chemesthesis

Testing oral chemesthetic thresholds is difficult due to the presence of sensitization, desensitization and SIR. Typical bias-free methods used to establish threshold sensitivity, such as forced-choice, ascending and descending staircase approaches, cannot be used because they require repeated stimulation. As discussed above, a short inter-stimulus interval can result in sensitization leading to confounded threshold determinations. Conversely, with a longer inter-stimulus interval, desensitization can result leading to detection thresholds that are artificially high. Allowing time for recovery from desensitization is potentially possible, however, in some cases this phenomenon has been shown to last for days (Albin et al., 2007; Green 1996; Karrer and Bartoshuk 1991). Moreover, long inter-stimulus intervals require subjects to remember preceding stimulus intensities and memory effects have been shown to worsen performance on discrimination tasks (Avancini de Almeida 1999; Cubero et al., 1995).

The limitations associated with investigating chemesthetic compounds restrict the options available for sound psychophysical testing. One potential solution that has been developed is the use of “half-tongue” methodologies (e.g. Dessirier et al., 1997; Simons et al., 1999) in which forced-choice, discrimination tasks are accomplished by placing a compound of interest on one side of a subject’s tongue and the control solution on the other. Subjects can compare the sensation on both sides of the tongue simultaneously to identify any intensity differences. Previous investigations have indicated no differences in sensitivity across both sides of the tongue as long as the same dorsal

lingual surface is being stimulated bilaterally (Lawless and Stevens 1988; 1990). Over several days, multiple stimulus concentrations can be compared to identify threshold sensitivity and, as the stimuli being compared are delivered simultaneously, memory effects are obviated.

Acknowledgements

Preparation of this chapter was supported in part by grants number R01 DC 002741 and R01 DC 005003 from the National Institute on Deafness and Other Communication Disorders (NIDCD), National Institutes of Health (NIH).

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Figure Legends

Figure 1. Showing trends in trigeminal (chemesthetic) and olfactory thresholds along lineal members of homologous series (plus some branched homologs), including alcohols, acetate esters, 2-ketones, alkylbenzenes, aliphatic aldehydes, and carboxylic acids. Also shown are both type of thresholds for cumene and selected terpenes. Trigeminal data are nasal pungency thresholds (NPTs) measured in anosmic subjects, and olfactory data are odor detection thresholds (ODTs) measured in normosmic subjects. A cut-off effect in chemesthesis detection (i.e., the saturated chemical vapor fails to elicit irritation) begins to develop for compounds whose NPTs are joined by a dashed line and fully develops for compounds whose NPTs are not plotted (see text). Bars indicate standard deviation.

Figure 2. Illustrating the similarity between nasal localization thresholds (NLTs) in normosmics and in anosmics for selected homologous n-alcohols, terpenes, and cumene (Cometto-Muñiz and Cain, 1998; Cometto-Muñiz et al., 1998b). Also shown, for comparison, are the nasal pungency thresholds (NPTs) (by definition, always obtained in anosmics) for the same chemicals. Bars indicate standard deviation.

Figure 3. Comparability between nasal pungency thresholds (NPTs) and eye irritation thresholds (EITs, in normosmics) for 22 VOCs from four homologous series, selected terpenes, and cumene (Cometto-Muñiz and Cain, 1991; 1995; 1998; Cometto-Muñiz et al., 1998b). Bars indicate standard deviation.

Figure 4. Depicting the similarity between eye irritation thresholds (EITs) measured in normosmics and in anosmics across 10 VOCs (Cometto-Muñiz and Cain, 1998; Cometto-Muñiz et al., 1998b). Bars indicate standard deviation.

Figure 5. Relationship between observed (i.e., experimentally measured) and calculated (from equation (2)) nasal pungency thresholds (NPTs). Both types of thresholds are plotted as $\log(1/\text{NPT})$, with NPTs expressed in units of parts per million (ppm) by volume. The dashed line represents the line of identity.

Figure 6. Chemical structures of three chemesthetic stimuli. A) The TRPV1 agonist capsaicin. B) The TRPM8 agonist WS-3, a simple menthane carboxamide. C) The KCNK, two-pore potassium channel blocker, alpha-hydroxy-sanshool.

Figure 7. Temporal patterns of oral chemesthesia. Repeated application of a chemesthetic irritant at short interstimulus intervals (e.g. 30 sec), elicits a sensitizing pattern of irritation in which the perceived sensation grows more intense until it reaches a plateau. When the repeated application of irritant chemicals occurs after a hiatus or at longer inter-stimulus intervals (greater than 5 min) desensitization occurs. However, desensitization can be overcome by recurrent stimulation at short inter-stimulus intervals. With continued stimulation, stimulus induced recovery (SIR) occurs and the perceived irritant sensation grows more intense.

Figure 8. Temporal profile and attribute identification following lingual application of a synthetic alkylamide. The figure shows the mean overall intensity perceived over time and the proportion of panelists selecting tingle, burning, cooling or numbing at each time point. Error bars indicate SEM. Figure adapted from Albin and Simons 2010.

FIGURE 1

FIGURE 2

FIGURE 3

FIGURE 4

FIGURE 5

FIGURE 6

A. Capsaicin

B. WS-3

C. alpha-hydroxy-sanshool

FIGURE 7

FIGURE 8