EDITORIAL

On the Scent of a Better World

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World events in 2001 have left many shocked and dismayed, yet we have much to look forward to. The Australasian Association for ChemoSensory Science (AACS) has resolved to offer the world's chemical senses community the opportunity to meet in Australia in December 2002 at unique, beautiful and inspiring Heron Island, on the Great Barrier Reef.

What might we expect ChemoSensory Science to produce in the foreseeable future? Here, ChemoSensory provides at least two answers from leading scientists. Our first review shows how chemesthesia works at a molecular level to elicit the oral and nasal sensations of hot and cold. This knowledge provides new insights into flavour perception as well as into basic mechanisms of pain. Then we examine how cognition is affected by environmental odour and whether the practice of aromatherapy has any validity.

This issue marks five years of operation of the Centre for ChemoSensory Research. Its forward vision is to stimulate ChemoSensory Science to create a safer, healthier and more prosperous world.

Chemesthesia: Hot and Cold Mechanisms

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It has been 90 years since G. H. Parker first described a chemical sense distinct from the senses of gustation and olfaction, and responsible for the detection of chemical irritants. What Parker originally called the common chemical sense has since been redefined and renamed (Erbe, 1962; Greer et al., 1990), and is now referred to as chemesthesia, the sensory system responsible for detecting and initiating responses to chemical irritants.

We now know that the chemically sensitive free nerve endings originally described by Parker do not constitute an independent chemical sense, as he thought. Instead, these nerve endings are a subset of pain and temperature sensitive fibres belonging to the general somatic sensory system, and are found throughout the skin and mucosal membranes. Advances in the field during the past 5 years are now bringing us closer to understanding the molecular mechanisms underlying chemesthetic sensibility.

Trigeminal nerve mediated chemesthesia

In humans, chemesthetic sensibility is perhaps best exemplified by the chemosensitive branches of the trigeminal (Vth cranial) nerve innervating areas of the eyes, nose and mouth (see Figure 1, page 21). We stimulate our chemesthetic sense through these fibres any time we eat peppers, chew spearmint or cinnamon gum, smoke tobacco, or drink warm beverages (see Box).

Although free nerve endings from other cranial and spinal nerves also respond to chemical stimuli, most of the research on chemesthesia, especially as it relates to taste and smell, has involved trigeminal chemoreception in mammals. The fibres of the trigeminal nerve that respond to chemical stimuli are referred to as polymodal nociceptors, responding to painful levels of thermal...
Chemesthesis: Hot and Cold Mechanisms continued

The diagram illustrates the trigeminal nerve and its branches, showing the distribution of sensory neurons involved in chemesthesis.

Chemical stimulation of trigeminal fibres in the cornea and the nasal and oral cavities leads to a variety of sensations, and are usually described using physiologically tangible words such as auras, stinge, tingle, prickle, bite, sting, or pain. Certain chemicals such as capsaicin, the active ingredient of hot peppers, and menthol cause sensations best described using thermal descriptors such as warm, hot, cool, chill, or cold.

Transduction mechanisms:
Trigeminal nerve fibres are found within or below epithelial layers, making them less accessible to incoming stimuli than olfactory or gustatory receptors. In between epithelial cells, some of these fibres extend virtually to the surface of the epithelium, stopping only a few micrometres from the surface, below the line of tight junctions. Therefore, in order to stimulate trigeminal nerve endings, chemical stimuli must first travel through either the lipid phase of epithelial cell membranes, or through the aqueous phase of epithelial tight junctions. Hydrophobic irritants primarily use the lipid phase, and lipid solubility is an important factor for the efficacy of hydrophobic irritants in the eyes, nose, and mouth.

Of course, trigeminal irritants are not limited to hydrophobic compounds. A broad range of compounds with diverse chemical structures and properties has been shown to stimulate trigeminal nerve fibres. This observation necessitates the existence of a diverse set of

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That Unmistakable Tingle...

The ‘tingle’, ‘fizz’ and ‘sling’ that we associate with carbonated drinks are classic examples of sensations arising from the chemesthetic sense. Most adults consider these sensations pleasurable, despite the fact that they are irritating and sometimes painful. Anyone who has ever had the experience of a flat soda knows that without the chemesthetic component, a soda is really nothing more than just sweetened, colored water.

So just how does carbonation cause stimulation of the trigeminal nerve? Recent experiments suggest a key role for intraepithelial acidification. Both in the oral and nasal cavities, carbon dioxide has been shown to activate trigeminal nerve endings via a carbonic anhydrase mediated pathway.

\[
\begin{align*}
\text{CO}_2 + \text{H}_2\text{O} & \leftrightarrow \text{HCO}_3^- + \text{H}^+ \\
\text{Membrane of Trigemina Nerve Ending} & \\
\text{P2X} & \\
\text{VR-1} & \\
\text{ASIC} & \\
\end{align*}
\]

In the epithelial tissues of the oral and nasal cavities, the ubiquitously present enzyme carbonic anhydrase converts CO₂ to carbonic acid, transiently acidifying epithelial tissues. Liberated protons are then free to interact with acid-sensitive membrane bound receptor proteins on intraepithelial trigeminal fibers. Experimental results suggest that the vanilloid receptor (VR1) is at least partially responsible for the nasal trigeminal response to CO₂ gas. It is likely that acid-sensing ion channels (ASIC) and perhaps ionotropic purinoceptors (P2X) also contribute to CO₂ sensitivity.

Receptive mechanisms, of which only a handful are currently known. Chemically, the vanilloid receptor has been used in reference to the chemoreceptive fibers of the trigeminal nerve, and the actual mechanisms of interaction between these fibers and environmental chemical stimuli are at best only partially understood.

So how exactly does a chemical irritant activate free nerve endings? A potentially irritating chemical compound that has penetrated outer epithelial layers can act either directly or indirectly on the membranes of trigeminal nerve endings. Depolarization of these nerve endings is the initial step to the sensation of irritation and pain, and any mechanism used by a chemical irritant that can lead to the appropriate level of depolarization will lead to the production of action potentials in the nerve. It does not matter if the transduction is through a direct interaction with a specific membrane bound receptor, or if it is through an indirect secondary mechanism.

Currently, the best understood example of direct chemical activation of trigeminal nerve endings is arguably that of the capsaicin receptor. Transduction of capsaicin, the active ingredient in chili peppers, is mediated via a capsicain-activated channel that is found in the small to medium size sensory neurons of the trigeminal ganglion. This channel has recently been cloned and sequenced (Caterina et al., 1997). Capsaicin contains a vanilloid moiety, and therefore this receptor is known as the vanilloid receptor, VR1. The activation of VR1 by capsaicin leads to a depolarization in the nerve ending that is subsequently detected by voltage-sensitive calcium channels in the ending and transmitted centrally. The VR1 is an excellent example of a polymodal receptor, being

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sensitive to not only capsaicin, but also moderate heat and low pH (Tominaga et al., 1998). The receptor's sensitivity to low pH and heat fit nicely with its role as a monitor of the physiological conditions of peripheral tissue.

Why does this receptor respond to capsaicin? The answer is not known, and thus the search is on for the body's endogenous capsaicin molecule. This search has focused mainly on lipophilic compounds, due to the hydrophobic properties of capsaicin (Promell, 2001). Capsaicin seems to interact with a cytosolic component of the VR1 receptor, and not with the extracellular domain as was previously assumed (Ivanyi et al., 2000), suggesting that the endogenous capsaicin molecule should be sought inside the cell. The small molecule itself is a polytopic protein containing six transmembrane domains. This protein forms a non-selective cation channel in the membrane that is functionally related to members of the transient receptor potential (TRP) family of excitatory ion channels (Catania et al., 1997).

The VR1 is not the only example of a polymodal receptor. Very recently, a close molecular cousin of the VR1, the cold-menthol receptor (CMHR1) has been identified that is activated by both menthol and cool temperatures (McKemy et al., 2002). The CMHR1 is yet another illustration of how a plant product like menthol can act on the chemesthetic sense to create a thermal sensation. Similar to the action of capsaicin and the burning hot sensation associated with it, chemical stimulation of CMHR1 by menthol and related compounds leads to a cooling sensation. This CMHR1 is also a member of the TRP family of excitatory ion channels, and interestingly, a significant proportion of CMHR1 expressing neurons also express VR1, giving those cells a distinct temperature responsive range (McKemy et al., 2002).

In addition to the VR1 and CMHR1, several other receptors have been identified in trigeminal nerves. Not all trigeminal sensitivity is low pH in the peripheral tissues is accounted for by the pH sensitive VR1, and the acid-sensing ion channel 1 (ASIC1) appears to also contribute to the pH sensitivity of peripheral tissues (Lange et al., 1997). Specific subtypes of several receptors for odour-sensitive compounds such as ATR, formyl peptide (FP), and acetylcholine also appear to be expressed in trigeminal nerves.

In the case of receptors for acetylcholine, trigeminal nerve endings appear to express more than one specific subtype of the neuronal nicotinic acetylcholine receptor (nAChR) (Almeida-Mannelli & Silver, 2000). These receptors also mediate our chemesthetic sensitivity to nicotine, a potent trigeminal stimulating causing sensations of tingling and burning. What role specific nAChRs play in the pain pathway, and the specific functional contributions each different receptor subtype makes remains to be determined.

The fact that many irritant compounds are also lipophilic suggests another possibility for direct activation of trigeminal nerve endings, although not through a receptor mediated pathway as is the examples previously described. Lipid solvents may depolarize nerve endings by causing physical damage to the lipid bilayer of the trigeminal nerve endings, creating the opportunity for ion flux through the damaged membrane (Bryan & Sorkin, 2000). Alternatively, exposure of a nerve ending to a lipid solvent may lead to the formation of discrete ion channels in the membrane, leading to ion flow through the disrupted lipid phase. In either case, ion flow can lead to a depolarization which may be transmitted centrally.

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for some irritating stimuli, a direct interaction with a receptor is not required. Instead, these compounds activate trigeminal nerve endings indirectly. Upon penetration of epithelial layers, these potential irritants must be peripherally metabolized in order to produce an active irritant. The best example of indirect activation is perhaps that of CO₂. This relatively inert compound readily activates trigeminal nerve endings upon penetration of epithelial layers. In an aqueous environment, CO₂ slowly dissociates, producing proton and bicarbonate ions. This dissociation is catalyzed by the action of carbonic anhydrase, an enzyme present in the epithelium of the nose and mouth, and also in the endothelium of the cornea (see box). Data suggest that carbonic anhydrase activity is essential for the trigeminal nerve response to CO₂ in carbonated beverages. (Korni & Bryant, 1993) and in the nasal detection of CO₂ gas. (Alammandi & Silver, 2002). In the case of nasal sensitivity to CO₂ gas, data implicate the V1, although it is probably not the sole and sensitive receptor mechanism at work. Blocking the nasal trigeminal sensory nerves does not lead to a complete block of the response to CO₂ gas, suggesting that other olfactory receptors, such as the acid-sensing ion channels (ASIC) and perhaps the intrinsic afferent receptors (FERX), also contribute to CO₂ sensitivity. (Alammandi & Silver, 2002).

Currently, carbonic anhydrase mediated sensitivity to CO₂ is probably the best understood example of indirect trigeminal nerve activation. The extent to which indirect activation via peripheral metabolism is involved in chemesthesia remains to be clarified, but more likely, indirect activation is the mechanism by which many known irritants release their chemesthetic properties. Pruritogens, aldehydes, ketones, and esters, such as benzylidene cyclohexanone, and ethyl acetate may be working through peripheral metabolism and the enzymatic liberation of proton, alcohol, and other irritants.

Trigeminal protection: withdraw and dilute

So why have animals evolved this chemosensory system, and why is it necessary? Unlike the olfactory and gustatory systems, the major role of trigeminal chemesthesia is to signal potentially or actually harmful skin and mucosal conditions, and to trigger adaptive behavioral and physiological responses. For chemesthetic trigeminal stimulation, the chemical source may be either internal or external. Internally, endogenous compounds released during tissue damage and chemicals associated with tissue conditions such as inflammation can lead to activation of trigeminal nerve endings.

Externally, the chemesthetic sense does not function as a long-range detector, as does the olfactory system. In fact, most trigeminal stimuli activate the trigeminal nerve at levels that are several log units more concentrated than the concentration required for activation of olfactory receptors. Essentially, trigeminal chemesthesia does not present nasal exposure to harmful chemicals, but once that initial exposure occurs, the chemesthetic sense functions to reduce further contact. In this aspect, the trigeminal chemesthetic system in mammals operates more like the gustatory system, i.e., it is a short-range detector of chemical stimuli.

Chemicals that excite trigeminal chemoreceptors can potentially produce chemesthetic pain and trigger protective reflex movements of rejection or withdrawal (Kremer et al., 1988). These reflexes are amongst some of the strongest reflexes of the body and probably evolved in animals as a way to minimize exposure to noxious substances and to perhaps hinder or discourage the consumption of potentially toxic food. The aversive movements associated with chemesthetic activation primarily serve to remove or further contact with the offending stimulus, and include restriction of the nares, and blinking of the eyes.

In addition to aversive and rejection movements, trigeminal activation elicits a variety of adaptive physiological responses, including local changes in vascular physiology (Hohler, 1988; Sudačan, 1996). Some of these tissue defensive responses include decreased respiratory rate, apnea, increased myocardial activity, vasodilatation, and plasma leakage. Responses such as increased salivation, increased nasal secretion, increased bronchial tone, and sweating tend to dilute the offending chemical irritant and to help remove it from sensitive tissues.

Sensory effector action

While activation of some of these physiological responses mentioned above may be due to trigeminal activation of autonomic fibres, other responses appear to be mediated by the sensory effector action of the trigeminal nerve, through the process of axon reflex (Finger et al., 1993). (See figure 2.) One subset of capsaicin sensitive trigeminal fibres secretes the vasoactive neuropeptides Substance P (SP) and calcitonin gene-related peptide (CGRP) upon stimulation. Stimulation of these peptidergic fibres results in the generation of a signal that is sent towards the trigeminal ganglion and the central nervous system. In the process of axon reflex, this signal can also result in retrograde excitation of other branches of the axon, resulting in neuropeptide release from all branches of the affected axon, leading to local vasodilatation and plasma leakage. The tissue defensive actions of this class of neuropeptides have led them to be called nociceptors (Kogur, 1988).

Specifically, in the mouth, capsaicin-sensitive sensory fibers have been shown to mediate extravasation (Bryant & Morse, 1993), vasodilatation (Ishii & Karita, 1994), and increased salivary flow (Takahashi et al., 1995). Interestingly, evidence from several experiments suggest that an trigeminal stimulation may potentially modify the function of the gustatory system (Wang et al., 1995, Osada et al., 1997, Isakoff & Sensoy, 1988).

Similarly, local release of neuropeptides upon nasal trigeminal stimulation has been shown to modify olfactory system function. Trigeminal stimulation decreases responses from olfactory receptor neurons (Bouret et al., 1987). This action is probably due to the local release of substance P from peptidergic nerve endings, since substance P has been shown to directly inhibit olfactory receptors (Bouret et al., 1988). Trigeminal stimulation also affects olfactory bulb function. Substance P and CGRP-containing trigeminal nerve fibres are known to innervate

![Figure 2](https://via.placeholder.com/150)

The process of axon reflexes. Upon sensory stimulation, peptidergic fibers send a signal to the central nervous system, which then travels to the olfactory branches of the same axon through retrograde excitation. This axon reflex may cause the release of neuropeptides such as Substance P and CGRP, which release tissue defensive actions such as vasodilatation and vasodilatation.

the olfactory bulb, extending as far as the glomerular layer (Finger & Botere, 1985). Some of these same fibers are collateral branches of nerve fibers found within the nasal mucosa (Schwab et al., 2002). This suggests that modulation of the olfactory bulb by trigeminal stimulation may be axon reflex mediated, bypassing involvement of a relay through the trigeminal sensory nuclei found in the brain stem.

cont. pg 9
Effect of Oils on Mental Performance

an oil had a large influence on the effect that an oil had on an individual’s performance during a cognitive task. During this experiment participants had to undertake the same choice reaction time task as before and, in addition, were asked to rate the oil presented to them on a visual analogue scale ranging from 1-very unpleasant to 7-very pleasant.

The results again showed that lavender essential oil had a sedative effect on participant’s performance during a cognitive task. The sedative effect increased with the hedonic appreciation of the oil. It was concluded that cognitive mediation appears to occur during perception. The hypothesis that lavender essential oil would significantly reduce performance on a cognitive task if considered to be hedonically pleasurable was unequivocally supported. This cognitive evaluation apparently takes place even when no recognition of the oil during the task is acknowledged.

The third experiment seemed to unfold more questions that it answered. It was unclear at this stage whether cognitive mediated effects stopped at the simplest level of hedonic evaluation or whether hedonic evaluation represented other cognitive factors such as cultural influences, expectations, and beliefs. Alternatively, it may be hypothesized that these other cognitive factors were additional to the role of perceived hedonic quality.

Cultural Variables

Experiment four tested whether cultural differences would affect individuals’ responses to particular odours and whether these differences would be realised in terms of cognitive performance.

Historically, olfactory researchers have suggested that culture plays a significant role in the interpretation of, and subsequent reaction to, certain odours (Clasen, 1995). In Experiment four two nationalities were compared, British and Australian adults. Two odours were examined, a native Australian oil (eucalyptus) and the popular British oil, lavender. It was hypothesised that Australians would be more influenced by the presence of eucalyptus oil and British participants more strongly influenced by the lavender. It was felt that stronger associations would be present with the culturally congruent odour and that these associations would lead the participant to have stronger prior expectations and beliefs regarding the likely effect of the particular oil.

In this experiment participants were asked to complete two cognitive tasks. The first of these was a simple vigilance task where the participant had to track a cursor on a computer monitor and respond by pressing the enter key when the cursor ‘skipped’ a space. The second, more complex cognitive task involved grammatical reasoning in which the participant had to respond either ‘true’ or ‘false’ to a number of pairs of statements such as ‘It is followed by A [BA].’

Results

Overall, the results showed that the presence of lavender decreased performance and eucalyptus oil increased performance on a cognitive task. However, no between group differences (cultural) were identified.

A number of possible interpretations of these findings exist. Firstly, the two groups were culturally too similar: nationality may not be an adequate operational definition of culture due to the ‘homogenisation’ of these two Western societies. Secondly, while neither group have well defined cultural roots, they share much of their culture in common (Anglo-Celtic). Thirdly, it was questioned whether differences in odour perception due to nationality and culture are still as strongly apparent in society today as historical literature suggests they have been in the past.

A second hypothesis was tested in Experiment four that examined whether the effect of the odours observed was dependent upon the type of cognitive task performed.

Results showed that significant differences between the odour conditions were only found during low order vigilance cognitive tasks and not during a high order cognitive task such as grammatical reasoning. This fascinating finding may provide an explanation as to why previous studies have produced seemingly conflicting results: the effects of odours on cognitive performance may be heavily task dependent.

Further experimental investigations are required to understand the cognitive processes underlying the evaluation of olfactory stimuli and how these impinge on certain cognitive tasks. It was considered appropriate to extend the previous investigations into individual differences to test whether other factors such as expectations and beliefs would influence the effects that essential oils had on cognitive performance.

Experiment five tested whether an individual’s expectation about the effects of lavender essential oil would vary the observed influence that the odour had on cognitive performance.

cont. pg 10