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Review Article

Chemogenic Subqualities of Mouthfeel

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Abstract

Mouthfeel refers to the physical or textural sensations in the mouth caused by foods and beverages that are essential to the acceptability of many edible products. The sensory subqualities contributing to mouthfeel are often chemogenic in nature and include heat, burning, cooling, tingling, and numbing. These "chemesthetic" sensations are a result of the chemical activation of receptors that are associated with nerve fibers mediating pain and mechanotransduction. Each of these chemesthetic sensations in the oral cavity are transduced in the nervous system by a combination of different molecular channels/receptors expressed on trigeminal nerve fibers that innervate the mouth and tongue. The molecular profile of these channels and receptors involved in mouthfeel include many transient receptor potential channels, proton-sensitive ion channels, and potassium channels to name a few. During the last several years, studies using molecular and physiological approaches have significantly expanded and enhanced our understanding of the neurobiological basis for these chemesthetic sensations. The purpose of the current review is to integrate older and newer studies to present a comprehensive picture of the channels and receptors involved in mouthfeel. We highlight that there still continue to be important gaps in our overall knowledge on flavor integration and perception involving chemesthetic sensations, and these gaps will continue to drive future research direction and future investigation.

Key words: carbonation, chemesthesis, flavor, mouthfeel, nociceptor

Mouthfeel is a term used to describe the varied physical or textural sensations in the mouth that are linked to foods and beverages. Along with taste and smell, mouthfeel contributes to food flavor (Kemp et al. 2009) and is important to product acceptability and liking (Guinard and Mazzucchelli 1996). Although mechanosensitivity underpins much of mouthfeel, a number of subqualities have been described (Bertino and Lawless 1993; Guinard and Mazzucchelli 1996) that are elicited through the chemical activation of oral somatosensory pathways, including commonly recognized sensations associated with carbonation (e.g., tingling), capsaicin (e.g., spicy/burning), menthol (e.g., cooling), and Szechuan peppercorns (e.g., tingling and numbing). These chemogenic mouthfeel sensations are the focus of the current review. With advances in molecular and cellular biology, the mechanisms subserving these mouthfeel sensations have been delineated and provide a neural correlate for these important perceptual events.

Chemesthesis is used to define the chemical sensibility of the skin and mucous membranes (Green and Lawless 1991; Green 1996). Initially regarded as a chemical irritant warning system, this view has evolved as the diversity of sensations evoked by chemesthetic compounds have been described (Green 1996). Indeed, many compounds found in foods, beverages, and spices can chemically activate receptors on nerve fibers that convey sensations of heat, burning, cooling, tingling, or touch (Bryant and Mezine 1999; Carstens 2016; Slack 2016). These chemesthetic compounds are found in many plant oils and extracts (Meotti et al. 2014) and thought to repel pathogens,

such as fungi, to prevent predation from herbivores (Pichersky and Gershenzon 2002), and/or to attract parasitoids as a defense mechanism after attack (van Poecke et al 2001). These compounds are important not only for the protection of plants from invaders but also serve as chemical cues for animals, where their detection is essential in order to identify and avoid consumption of potentially noxious or harmful compounds. Accidental or intended exposure to these compounds can prompt nocifensive responses, such as sneezing, salivation, coughing, or rubbing the affected areas. These nocifensive responses to chemesthetic compounds are proposed to be part of a "chemofensor" complex and are well characterized in the oral and nasal mucosa (Green 2012). Of course, over time individuals can learn to like and seek out "spicy" foods, despite the irritation associated with the presence of these compounds (Byrnes and Hayes 2013).

Chemesthesis, by definition, is multimodal, due to the potential activation of multiple chemically sensitive receptors, which can signal several different afferent pathways and communicate sensations of irritation, pain, temperature, and touch in the oral cavity (Roper 2014). Multiple receptor types expressed on sensory nerve fibers serve to detect chemesthetic compounds that can contribute to mouthfeel associated with foods and beverages. Many trigeminal sensory nerve fibers, and lingual keratinocytes, express a variety of chemosensory receptors that encode heat, cold, pain, tingling, and numbing sensations to provide information, in addition to taste and smell, about the chemical composition of foods and beverages.

Mouthfeel: carbonation

The tingling sensation associated with carbonated drinks is highly sought after and contributes to the mouthfeel and enjoyment of beverages, including beer, champagne, and soft drinks. Recently, carbonation was shown to enhance the thirst-quenching properties of water (Peyrot des Gachons et al. 2016). In novel applications, carbonation has been used to develop new food products purported to increase appeal toward children, (Botelho 2007) including carbonated dairy products (e.g. Go-Gurt Fizzix or MacFarms e-Moo) and fruits (Fizzy Fruits). Although the appeal of carbonated products has long been observed, only recently have advances been made in understanding the mechanism underpinning the fizzy sensation.

The tingle sensation associated with carbonated beverages is often mistakenly attributed to the bursting of carbon dioxide (CO_2) bubbles on oral tissues and subsequent activation of tactile pathways (Yau and McDaniel 1990, 1992). However, accumulating evidence suggests that the carbonation sensation is primarily of chemogenic origin (Green 1992; Komai and Bryant 1993; Simons et al. 1999, Dessirier et al. 2000a; Wise et al. 2013) and that bubbles per se play only a minor role in shaping perceived intensity (Wise and Bryant 2014). Indeed, no difference in perceived tingle intensity was noted in panelists evaluating carbonated water at normal atmospheric pressure (0 atm) and again in a hyperbaric chamber where atmospheric pressure was regulated to 2 atm and prevented bubble formation (Wise et al. 2013). These results clearly demonstrate that mechanical activation of tactile pathways by bursting bubbles is not required to evoke the tingle sensation associated with carbonated beverages. What then underpins carbonation-evoked tingling?

Carbonation: chemogenic origin

Insights to this question first came to light in the early 1960s when Swedish scientists reported that the "prickly feeling of carbonated drinks" was absent when subjects were given carbonic anhydrase inhibitors (Hansson 1961). This relatively obscure report was referenced and corroborated in 1988 when researchers reported that carbonic anhydrase antagonists taken for the prevention of acute mountain sickness eliminated the tingle sensation accompanying a celebratory bottle of beer—the "champagne blues" (Graber and Kelleher 1988). Carbonic anhydrase is an enzyme that catalyzes the conversion of CO_2 and water into carbonic acid. Reducing the tingling sensation of carbonated water by preventing the formation of carbonic acid, therefore, implicates a mechanism by which oral tissue acidification is detected by the activation of nociceptive nerve endings in the oral mucosa. Pioneering physiological studies in the 1990s confirmed that carbonated water solutions activate nociceptive fibers in the lingual nerve (Komai and Bryant 1993) as well as second-order, wide-dynamic range neurons in superficial layers of the trigeminal caudalis (Vc; Simons et al. 1999). Lingual nerve recordings indicated that CO_2-sensitive fibers typically responded to other noxious stimuli, including heat (55 °C), cold (8 °C), and acids (HCl and NH4Cl). Similarly, single unit recordings from neurons in Vc showed broad sensitivity to noxious thermal (54 °C), chemical (HCl, pH 1) and mechanical (pinch) stimuli. Consistent with the hypothesis that the tingle sensation evoked by carbonated water is of chemogenic origin, neural activity in lingual nerve fibers and central caudalis neurons was reversibly inhibited by pretreatment with carbonic anhydrase inhibitors acetazolamide (Komai and Bryant 1993) or dorzolamide (Simons et al. 1999), respectively. Further support for the chemogenic nature of carbonated water-evoked sensations comes from studies utilizing c-Fos immunohistochemistry— an anatomical marker of cellular activity. Although freshly opened carbonated water delivered to the tongue elicited c-Fos expression in superficial neurons of the rat dorsomedial Vc, pretreating the tongue with dorzolamide (Simons et al. 1999) or acetazolamide (Dessirier et al. 2000a) significantly reduced the number of fos-positive cells identified in this same region.

Correlative psychophysical studies have been completed in an effort to link the physiological findings in animal models to human perception. Early studies showed perceived tingle intensity to be a function of CO_2 concentration (Cometto-Muñiz and Noriega 1985; Yau and McDaniel 1990, Green 1992; Harper and McDaniel 1993). More recently, the role of carbonic anhydrase in mediating CO_2-evoked tingle has been confirmed in controlled studies. In a sensitive half-tongue, forced-choice procedure, topical pretreatment of the dorsal lingual surface with dorzolamide (Simons et al. 1999) or acetazolamide (Dessirier et al. 2000a) reduced the perceived tingle sensation evoked by carbonated water solutions flowed over the tongue. Interestingly, in the former study, dorzolamide pretreatment reduced perceived tingle intensity only when carbonated water flowed over the dorsal surface of the tongue for 5 but not 15 s. These results suggest that with prolonged application, CO_2 is able to penetrate into deeper tissue layers where topical dorzolamide was unable to reach, thus enabling the conversion of CO_2 into carbonic acid with the subsequent activation of deeper nociceptive neurons.

Until recently, the specific receptor mechanism responsible for transducing the presence of carbonic acid into a nociceptive neural signal was unknown. Several receptors are known to respond to acids including the acid-sensing ion channels (ASICs; Lingueglia et al. 1997; Waldmann et al. 1997) and transient receptor potential (TRP) channel V1 (Caterina et al. 1997; Tominaga et al. 1998). These receptors are expressed in peripheral nociceptive cells and are activated by the binding of extracellular protons. Such a mechanism would require the presence of extracellular carbonic acid that would enable the local conversion of CO_2 to carbonic acid. However, most forms

of carbonic anhydrase are cytoplasmic (Supuran 2007) and several have been identified in trigeminal nociceptive nerve endings (Bryant 2000). Additionally, CO_2 is lipophilic and easily passes through cellular membranes (Endeward et al. 2014). Recent evidence suggests that CO_2 is converted to carbonic acid intracellularly where acidification subsequently activates TRPA1 (Wang et al. 2010). Acids applied extracellularly to TRPA1-expressing human embryonic kidney cells elicit no response, whereas CO_2 applied in the same manner activates these cells (Wang et al. 2010). However, when inside-out patches of TRPA1-expressing cells are used in patch-clamp experiments, acids applied to the cytoplasmic face strongly activate this receptor. Thus, cytoplasmic carbonic anhydrase and TRPA1 receptors are key elements underpinning carbonation tingle.

Carbonation: sensation modulation

The sensation elicited by carbonated water is not static but is influenced by the temperature and duration of stimulation, stimuli presented simultaneously or prior to CO_2, and the presence of bubbles. As many consumers of carbonated beverages can attest, the tingling/pungent sensation experienced when consuming a cold beverage differs from that when consuming the same beverage at room temperature. This effect is independent of the ability of cold solutions to dissolve higher concentrations of CO_2 (Green 1992; Wise and Bryant 2014). Multiple controlled studies have verified these anecdotal reports and have indicated that reducing the serving temperature of carbonated solutions below the temperature of the tongue increases the perceived bite associated with these solutions (Green 1992; Yau and McDaniel 1991; Wise and Bryant 2014). In general, carbonated solution temperatures below 24 °C are perceived as increasingly more intense (Green 1992; Wise and Bryant 2014), whereas warming solutions to temperatures above ~40 °C have no impact (Wise and Bryant 2014). Interestingly, pretreating the tongue with the cold receptor (TRPM8; McKemy et al. 2002) agonist, menthol, had no apparent effect on the perception of carbonation-evoked tingle (Wise and Bryant 2014). Results from these studies indicate that the carbonation sensation is modulated by cold temperature and suggests a mechanism by which cold-sensitive fibers potentiate the CO_2-evoked signal (Andersson et al. 2004). That menthol pretreatment has no effect indicates that TRPM8-expressing cold-sensitive neurons do not mediate the cold-induced enhancement. A population of cold-sensitive neurons has been identified in mice that do not express TRPM8 (Munns et al. 2007) and provides a potential mechanism by which cold temperature, but not menthol, serves to modulate carbonation-evoked tingle sensations. Potential receptor candidates for this effect are TRPC5 (Zimmermann et al. 2011) or cold-sensitive potassium channels (reviewed in Lolignier et al. 2016).

In addition to serving temperature, the duration of exposure to carbonated water impacts the intensity of the perceived bite. When held in the mouth, carbonated solutions elicited a sensation that grew from nonpainful to painful within a 10-s exposure period (Green 1992). Similarly, when dipping the tongue into carbonated solutions, time intensity ratings of carbonation bite increased within 5 s to reach a peak between 10–15 s (Wise and Bryant 2014). Thus, over a relatively short interval of constant stimulation, it appears that carbonation-evoked bite shows a sensitizing pattern of response. This pattern could reflect spatial summation wherein the membrane-permeable CO_2 molecules penetrate into deeper lingual tissues to elicit activity in an increasing number of TRPA1-expressing neurons. Interestingly, as the exposure to carbonated solutions increased past 15 s, time intensity ratings of the carbonation bite began to plateau or decline (Wise and Bryant 2014). This is consistent with findings from earlier studies where carbonated water-evoked higher tingling sensations when subjects dipped their tongue into solutions for 5 s compared with 15 or 60 s (Dessirier et al. 2001). Thus, although carbonation bite increases with short continuous exposure, prolonged periods of exposure result in self-desensitization with a concomitant reduction in the perceived carbonation sensation. Although the mechanism underpinning CO_2-induced desensitization is unknown, other TRPA1 agonists have shown similar sensitizing–desensitizing patterns of irritation following continuous exposure (Simons et al. 2003, 2004).

Although bubbles are not a requirement to evoke the tingling sensation associated with carbonated beverages, the presence of bubbles can modulate the carbonation perception. When air is bubbled through solutions of carbonated water and directed at the tongue, the intensity of the carbonation bite is enhanced compared with the same solutions without the addition of air bubbles (Wise et al. 2013). Although still speculative, this heightened sensation is thought to result from improved mixing at the lingual interface that results in higher localized concentrations of CO_2. Further studies are needed to fully understand the mechanism.

The perceived intensity of the carbonation bite has been shown to be impacted by the presence of other stimuli presented prior to, or simultaneously with, exposure to carbonated solutions. Adding tastants to carbonated solutions has also been shown to modulate the perceived bite, however, not in an easily generalizable manner. Indeed, the sweeteners sucrose (Yau and McDaniel 1992 but see Cometto-Muñiz et al. 1987) and glucose (Hewson et al. 2009), but not fructose (Hewson et al. 2009), reduced the carbonation sensation. Conversely, carbonation reduced brain responses to sweeteners, particularly sucrose (Di Salle et al. 2013). Similarly, tartaric acid (Cometto-Muñiz et al. 1987) enhanced carbonation pungency whereas phosphoric acid had no effect (Yau and McDaniel 1992). Finally, the bitter compound quinine reduced the carbonation bite, whereas sodium chloride enhanced it (Cometto-Muñiz et al. 1987). Although the impact of tastants on carbonation perception is relevant to the food and beverage industry, these interactions have not been systematically explored.

Carbonation: taste

Although a minor constituent of the overall sensation, carbonation also elicits a sour taste in addition to the characteristic tingling. Sour taste is evoked by the activation of H^+-sensitive taste receptor cells. Results in Drosophila implicate the ionotropic glutamate receptor IR56d in mediating this gustatory response (Sánchez-Alcañiz et al. 2018), whereas in mammals, carbonation activates taste receptor cells expressing the heteromeric polycystic-kidney disease-like (PKD) potassium ion channels, PKD2L1 and PKD1L3 (Ishimaru 2006). Mice lacking PKD2L1 cells showed no chorda tympani nerve responses to CO_2 exposure (Chandrashekar et al. 2009). The sour taste associated with CO_2 exposure involves the activity of carbonic anhydrase (Chandrashekar et al. 2009; Lossow et al. 2017), in particular Car4, a specific isoform that is tethered to the extracellular surface of type III sour-sensing taste receptor cells coexpressing PKD2L1 (Chandrashekar et al. 2009; Lossow et al. 2017). Acidification of the extracellular surface, through the conversion of CO_2 to carbonic acid by Car4, results in the subsequent depolarization of these taste cells. Although the sour taste from carbonation is minor compared with the tingling sensation, it is clear that this sensation is an important contribution to the overall flavor of carbonated beverages.

Reciprocal interactions between carbonation and taste have also been described. Addition of CO_2 to taste solutions does not significantly increase overall taste intensity, however, the taste quality changes with sourness becoming a more prominent component (Cometto-Muñiz et al. 1987; Cowart 1998). Additionally, the modulatory effects of some tastants on CO_2 pungency likely have pronounced effects on the perception of sourness evoked by CO_2.

Mouthfeel: burning and heat pain

Of all the receptors implicated in chemesthesis, TRPV1 is the most commonly discussed. TRPV1 is expressed on sensory nerve endings, as well as epithelial cells (Marincsák et al. 2009), and is responsible for the burning sensations from chili peppers (capsaicin), ginger root (gingerols), and black pepper (piperine). TRPV1 is a cation channel that opens with sensitivity to noxious heat and chemical vanilloid agonists and is rapidly sensitized by algesic mediators after inflammation and tissue injury (Caterina et al. 2000; Davis et al. 2000). In human psychophysical studies, pretreating the tongue with capsaicin elicits a burning sensation that disappears over time (Dessirier et al. 1997; Green 1989, 1991a, 1991b). For a period of time afterward, subsequent capsaicin stimulations evoke no sensations, and corollary physiological experiments have shown that capsaicin-sensitive nerve fibers are desensitized and no longer responsive during this same period (Dessirier et al. 2000b). Interestingly, early reports indicated that desensitization is not predicted by the sensory irritancy evoked by vanilloids (Szolcsányi and Jancsó-Gábor 1976). During this period of desensitization, mechanical and cold sensitivity is still intact, whereas sensitivity to warm stimuli is impaired (Szolcsányi 1977). Desensitization appears to be receptor mediated and calcium dependent as repeated capsaicin application to trigeminal ganglion cells induced tachyphylaxis which was markedly reduced when extracellular Ca^{+2} was removed (Liu and Simon 1996). This period of desensitization can be overcome with repeated capsaicin applications at short interstimulus intervals (<2 min)—a phenomenon termed stimulus induced recovery (SIR). SIR has been observed at the neuronal level in animal studies (Dessirier et al. 2000b) as well as psychophysically in humans (Green and Rentmeister-Bryant 1998). Capsaicin is also well known to cross-desensitize the oral cavity to carbonated beverages (Dessirier et al. 2000a, 2001) among other chemesthetic agents, including mustard oil (Simons et al. 2003), nicotine (Dessirier et al. 1997), menthol (Cliff and Green 1996), sodium chloride, cinnamaldehyde, and ethanol (Green 1991b). Because capsaicin desensitization on the tongue also reduces the perceived bite from carbonated water (Dessirier et al. 2001), this suggests that a subgroup of capsaicin-sensitive nociceptors also expressing TRPA1 are involved in conveying carbonation-evoked signals from the periphery (Dessirier et al. 2001). Not unexpectedly, capsaicin is able to sensitize the lingual surface to heat pain (Green et al. 1986); however, TRPV1 agonists do not influence cold pain (Green 1986; Albin et al. 2008), suggesting that thermal and chemical triggering of TRPV1 have different temporal scales, thresholds, and/or sites of activation.

TRPV1 is also sensitive to ethanol and acids (extracellular protons), both of which are found in many alcoholic carbonated beverages. Mice that no longer express TRPV1 have altered preferences for ethanol (Blednov and Harris 2009), and application of ethanol on TRPV1-expressing cells potentiated responses to capsaicin and acidic solutions and lowered the threshold of TRPV1 activation (Trevisani et al. 2002). These data could potentially explain the phenomenon of the increased burning sensation when the consumption of spicy foods is combined with drinking alcoholic carbonated beverages. However, upon exposure to high doses of capsaicin, the oral irritation from carbonation decreases (cross-desensitization; Dessirier et al. 2001), suggesting that carbonated beverages activate a subset of cells coexpressing both TRPV1 and TRPA1.

In addition to carbonic acid, TRPA1 is activated by multiple pungent compounds, including mustard oil, wasabi (allyl isothiocyanate), garlic (allicin), onion (diallylsulfide), cinnamon (cinnamaldehyde), extra virgin olive oil (oleocanthal), methyl salicylate (commonly found in mints and gum), and carbonation (Bandell et al. 2004; Jordt et al. 2004; Bautista et al. 2005; Macpherson et al. 2005; Koizumi et al. 2009; Wang et al. 2010; Peyrot des Gachons et al. 2011, Nilius and Appendino 2013). Classically, TRPA1 agonists produce a burning sensation in the mouth and throat (Prescott and Swain-Campbell 2000; Simons et al. 2003). Mice lacking the TRPA1 receptor do not avoid water laced with mustard oil (Kwan et al. 2006), indicating that these compounds are inherently aversive in mammals. Many TRPA1 agonists also increase heat hyperalgesia when placed on skin or the oral mucosa including mustard oil and cinnamaldehyde (Albin et al. 2008; Koltzenburg et al. 1994), and similar reports have been made in behavioral studies with rodents (Tsagareli et al. 2010). Experimental results suggest there is much overlap between TRPV1 and TRPA1 expression in sensory neurons (Story et al. 2003; Kobayashi et al. 2005), suggesting a potential mechanism by which TRPA1 agonists and TRPV1 agonists can cross-desensitize. Alternatively, capsaicin desensitization may reduce the spontaneous activity of TRPV1-expressing cells that converge centrally onto neurons also receiving input from cells expressing TRPA1. Thus, during capsaicin desensitization, the integrated signal impinging on these second-order cells receiving both TRPV1 and TRPA1 input would be reduced.

Acids from foods and beverages can activate a number of proton-sensitive channels and receptors. TRP channels, including TRPV1 and TRPA1, are acid sensitive and evoke a burning sensation when activated. In addition, weak acids such as vinegar (acetic acid) can diffuse through cells in the oral and nasal cavities to activate TRPA1 intracellularly. ASICs are also sensitive to protons and are expressed on trigeminal ganglia (Fu et al. 2016), which are coexpressed with TRPV1 (Ugawa et al. 2005). The PKD-like ion channels PKD2L1 and PKD1L3 are also reported to be sensitive to changes in pH within the oral cavity (Ishimaru et al. 2006); however, these channels are not highly expressed in trigeminal ganglia. Other potential candidates for acidic trigeminal nerve activation include hyperpolarization-activated cyclic nucleotide-gated (HCN) channel 4 (Stevens et al. 2001) and 2-pore potassium channels (K2P), especially K2P5 (TASK-2; Lin et al. 2004). HCN4 is expressed in less than 10% of trigeminal neurons (Cho et al. 2009), but K2P5 is preferentially expressed in the peripheral versus central nervous system (Medhurst et al. 2001), making K2P-expressing neurons plausible targets for acid-induced irritation (see below).

Mouthfeel: cooling

The most highly cited cold transduction channel, TRPM8, is activated by cool temperatures (<25 °C) and the "cooling" compounds peppermint and menthol (McKemy et al. 2002; Peier et al. 2002). Recently another TRP channel has been implicated in cold transduction. TRPC5 is cold sensitive and is expressed on sensory neurons but does not respond to menthol application (Zimmermann et al. 2011). Although the chemosensitivity of TRPC5 has not been systematically explored, this receptor may serve a role in mouthfeel

sensations and could, for example, underpin the enhancement of CO_2-evoked bite by cold temperatures.

Interestingly, TRPA1 has also been implicated in detecting temperatures that are less than 20 °C (Bandell et al. 2004; Sawada et al. 2007). Because mice lacking this receptor have deficits in cold nocifensive behaviors when exposed to surfaces below 0 °C (Karashima et al. 2009), this channel is purported to have some involvement in sensing cold pain. However, other studies using transgenic cell lines and in vitro studies have challenged this notion (Caspani and Heppenstall 2009). Many studies have found that compounds that activate TRPA1 increase cold pain for humans (Namer et al. 2005) as similarly seen in rodent models (Tsagerali et al. 2010). Collectively, these results suggest that TRPA1's involvement in cold transduction may (i) not be easily realized in culture or (ii) may have roles in chemesthesis that are reflected more viscerally (Fajardo et al. 2008). Thus, food and spices containing TRPA1 agonists, including carbonation, could theoretically potentiate both heat and cold sensations in the oral cavity in addition to the chemesthetic sensations of burning and stinging through the TRPA1 channel. Evidence for this has been observed in human studies where high concentrations of carbonation (6000 ppm) significantly increased ratings of cold elicited by a 4 °C stimulus (Green 1992).

Mouthfeel: tingle and numbing

Several chemesthetic compounds evoke numbing and tingling sensations on the tongue. Indeed, although most TRPA1 agonists elicit a burning sensation, CO_2 evokes a sensation described as tingling. Numbing compounds, such as lidocaine, block voltage gated ion channels, which inhibits the propagation of action potentials along nerve fibers. There is good evidence that protons (including those from CO_2) block NaV channels, which are highly expressed in the mammalian peripheral nervous system (Khan et al. 2002). Interestingly, some naturally occurring compounds produce tingling sensations when ingested. Hydroxyl sanshool, from Sichuan peppercorns (*Xanthoxylum piperitum*), evokes a sensation described as similar to a weakly carbonated beverage (Bryant and Mezine 1999). Spilanthol from jambu fruit (*Acmella oleracea*) elicits a similar sensation. Sanshools were reported to excite a variety of different peripheral afferent fibers including those from low-threshold mechanoreceptors, thermoreceptors, and nociceptors (Bryant and Mezine 1999; Lennertz et al. 2010) as well as spinal wide-dynamic range-type neurons (Sawyer et al. 2009). Sanshool compounds inhibit 2-pore potassium (K_{2p}) channels, including K2P3, K2P9, and K2P18 (KCNK3, KCNK9, and KCNK18, respectively; Bautista et al. 2008), which are responsible for maintaining the resting membrane potential and determining nociceptor excitability (Plant 2012). These particular KCNK channels appear to have high expression levels in human trigeminal ganglia (Flegel et al. 2015). It should be noted that sanshools, and related compounds, have also been purported to activate TRPA1 and TRPV1 channels (Sugai et al. 2005; Koo et al. 2007; Klein et al. 2011). In addition, pungent compounds, including piperine from black peppercorns (*Piper nigrum L*), capsaicin from chili pepper (*Capsicum annuum*), polygodiol from mountain pepper (*Tasmannia lanceolata*), and 6-gingerol from ginger (*Zingiber officinalis*) can also inhibit KCNK3, KCNK9, and KCNK18 channels (Beltrán et al. 2013; Beltrán et al. 2017), implying that irritant compounds can activate some populations of nociceptive neurons that transduce signals of tingling. It appears that blocking NaV and/or K2P channels, perhaps in combination with the activation of TRPV1 or TRPA1, may help explain the paresthesia sensations on the tongue associated with tingling compounds and/or drinking carbonated beverages.

Mouthfeel: kokumi and mouthfulness

Recently, the term 'kokumi' has been used to describe mouthfulness, thickness, and/or complexity of foods. The literal translation of kokumi from Japanese comes from the combined words: rich (koku) and taste (mi). It is believed that certain γ-glutamyl peptides can activate a calcium-sensing receptor (CaSR) involved in the sensation of mouth and tongue coating from foods containing butter or fatty emulsions (Yamaguchi and Ninomiya 1998; Ohsu et al. 2010). These peptides can be commonly found in yeast extracts, cheeses, green beans, garlic, and onions, and have been shown to enhance saltiness and savoriness of other foods (Toelstede and Hofmann 2009; Dunkel et al. 2007; Ueda et al. 1990). Many γ-glutamyl peptides, including γ-glutamyl-cysteinyl-glycine (reduced form of glutathione) and γ-glutamyl-valinyl-glycine activate CaSRs expressed on type II (receptor cells) and type III (presynaptic) taste cells, which are distinct from cells responsible for umami and sweet taste transduction (Maruyama et al. 2012). These data parallel the observation that various extracellular CaSR agonists have been known to enhance sweet, salty, and umami tastes; however, none of these molecules have a distinct taste themselves. The sensory characteristics of kokumi may also have a chemesthetic origin. Recent data suggests that lingual application γ-glutamyl-valinyl-glycine can elicit calcium responses in a small population of trigeminal ganglion neurons (Leijon et al. 2019). These data suggest that kokumi-inducing peptides may alter taste information by activation of gustatory and trigeminal pathways, an exciting area for further exploration.

Future research directions

Chemical sensitivity of the trigeminal nerve contributes to mouthfeel and flavor to influence the enjoyment of food and beverages. Over the last few decades, several molecular channels and receptors have been identified that underpin these sensations by detecting relevant chemesthetic compounds in peripheral tissues. These same channels and receptors subserve pernicious sensations including pain and itch. As such, there is increased need for further research. Future research should be aimed at mapping neural projections as they enter the brainstem and spinal cord, identifying and elucidating how relay neurons send information to higher order brain centers and ultimately how these changes in peripheral and central neuron excitability are perceived as distinct chemosensory sensations.

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