RUNNING HEAD: THE MYSTERY OF 'METAL MOUTH' IN CHEMOTHERAPY

REVIEW ARTICLE

The mystery of 'metal mouth' in chemotherapy

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Abstract

Of all the oral sensations that are experienced, ‘metallic’ is one that is rarely reported in healthy participants. So why, then, do chemotherapy patients so frequently report that ‘metallic’ sensations overpower and interfere with their enjoyment of food and drink? This side-effect of chemotherapy—often referred to (e.g., by patients) as ‘metal mouth’—can adversely affect their appetite, resulting in weight loss, which potentially endangers (or at the very least slows) their recovery. The aetiology of ‘metal mouth’ is poorly-understood, and current management strategies largely unevidenced. As a result, patients continue to suffer as a result of this poorly-understood phenomenon. Here, we provide our perspective on the issue, outlining the evidence for a range of possible aetiologies, and highlighting key research questions. We explore the evidence for ‘metallic’ as a putative taste, and whether ‘metal mouth’ might therefore be a form of phantageusia, perhaps similar to already-described “release-of-inhibition” phenomena. We comment on the possibility that ‘metal mouth’ may simply be a direct effect of chemotherapy drugs. We present the novel theory that ‘metal mouth’ may be linked to chemotherapy-induced sensitisation of TRPV1. Finally, we discuss the evidence for retronasal olfaction of lipid oxidation products in the aetiology of ‘metal mouth’. This article seeks principally to guide much-needed future research which will hopefully one day provide a basis for the development of novel supportive therapies for future generations of patients undergoing chemotherapy.

Keywords: Metallic, phantom, retronasal, TRPV1, chemesthesis, taste.

Introduction

A subset of chemotherapy patients report alterations to oral sensation as a side-effect during treatment, including a loss of sensation, distortions, and phantom sensations. Patients commonly report unpleasant, unexplained, persistent 'metallic' sensations in the mouth (Rhodes *et al*., 1994; McDaniel & Rhodes, 1998; Newell *et al.*, 1998; Wickham *et al*., 1999; Bernhardson, Tishelman, & Rutqvist, 2008; Jensen *et al.*, 2008; Rehwaldt *et al.*, 2009; Boltong, Keast, & Aranda, 2012; Coa *et al.*, 2015; IJpma *et al.*, 2015; IJpma *et al.*, 2017; Amézaga *et al.*, 2018) which are probably more qualitatively similar to 'metallic' sensations reported with metals such as iron or copper, as opposed to other metals such as calcium (which is more bitter) or sodium (which is more salty) (Richter & MacLean, 1939; Tordoff, 1996; Lawless *et al.*, 2003; Yang & Lawless, 2005; Lim & Lawless, 2005a; Omur-Ozbek & Dietrich, 2011). This 'metal mouth' phenomenon affects patients on multiple different treatment regimens, and there is no clear association with the platinum content of the drugs (e.g., IJpma *et al.*, 2017; Amézaga *et al.*, 2018).

Estimates of the prevalence of 'metal mouth' amongst chemotherapy patients vary (see Table 1), often depending on the study design. The lowest estimate of prevalence (9.7%) was reported by Bernhardson, Tishelman, and Rutqvist (2008). Here, the chemosensory descriptor "metallic" was seemingly not listed on the questionnaire sheet; patients had to provide the word themselves and list it under 'other' (cf. Lawless *et al.*, 2005, Experiment 3). Perhaps unsurprisingly, studies where the prompt word "metallic" is given to patients in advance have documented a higher prevalence range (≥15.7%). Studies also differ markedly in other aspects of their methodology, and the cancer types, drug regimens, and patient groups included (see Table 1). For example, one study only included patients with a history of chemotherapy-induced chemosensory disturbance (Rehwaldt *et al.*, 2009), and unsurprisingly reported the highest prevalence estimate, 78.4%. Sometimes "metallic" was the only descriptor that patients were able to select (e.g., Newell *et al.*, 1998), but sometimes alternative chemosensory descriptors, e.g., "blood taste", "bad taste", "chemical taste", were provided as options alongside "metallic taste" (e.g., Coa *et al.*, 2015; IJpma *et al.*, 2017; Amézaga *et al.*, 2018).

INSERT TABLE 1 ABOUT HERE

There is perhaps also a broader concern: namely, because "metallic taste" is often discussed amongst the chemotherapy patient community, there might be an element of suggestibility—where patients begin to interpret their sensory experience (which may be unfamiliar and hence

difficult to label) as whatever 'taste' is pre-selected for them (e.g., see Nitschke *et al*., 2006). This can be inadvertent: phrases such as "metallic taste" can simply slip into the vernacular (as discussed by Lawless *et al*., 2005). Patients suffering from a host of different individual sensory distortions may well already have been lumped together in the "metallic taste" category, thus potentially giving rise to an over-reporting bias. It may be instructive to investigate how patients who had been trained in the food industry describe the taste changes they experience during chemotherapy (as they are likely to have a broader vocabulary to label what is a new and unfamiliar sensory experience).

Whilst other taste changes in chemotherapy patients are probably linked to the death of taste cell progenitors in the affected modality (e.g., see Mukherjee & Delay, 2011; Jewkes *et al.*, 2018) the aetiology of 'metal mouth' is particularly curious because 'metallic' is not a widely-recognised modality of taste. There is no accepted 'metallic' taste receptor (but see Nelson *et al*., 2001; Riera *et al*., 2007; Riera *et al*., 2009a); although people do ascribe the descriptor 'metallic' to a particular kind of oral sensation (e.g., Lawless *et al.* 2005, Experiment 2; but see Lawless *et al.*, 2005, Experiment 3). In experimental situations, neurologically-healthy human participants can detect the presence of iron, copper, zinc, and other metals on the tongue (Zacarias *et al.*, 2001; Lawless *et al*., 2004; Lawless *et al*., 2005; Lim & Lawless, 2005b; Laughlin *et al.*, 2011), and detect the differences between different metals on a sensory basis (Laughlin *et al*., 2011; Omur-Ozbek & Dietrich, 2011; Piqueras-Fiszman *et al*., 2012). Although the phrase "metallic taste" is commonly used, how these well-known metallic sensations are actually transduced remains unclear.

In summary, "metallic" sensations in chemotherapy are commonly reported; they can severely distort patients' experiences of food (and linger after eating and drinking); and they are also entirely unexplained. Maintaining proper nutrition is undoubtedly vital in helping cancer patients withstand a punishing chemotherapy regime (see also Spence, 2017, on the importance of proper nutrition in the hospital setting). Distorted, lingering, unpleasant mouth sensations are linked to a loss of appetite and weight loss (Coa *et al*., 2015; Nolden *et al.*, 2019a; Nolden *et al.*, 2019b) and could potentially predispose patients to cachexia—the irreversible muscle wasting condition which accounts for an estimated 20% of cancer-associated deaths (Hong *et al.*, 2009; Blackburn, 2009). Here, we will provide our perspective on the poorly-understood 'metal mouth' side-effect of chemotherapy, discussing some possible causes of the metallic sensation and highlighting selected areas of the field for further investigation.

Background: chemotherapy is toxic and causes oral sensory loss

The 'metal mouth' sensation in chemotherapy occurs either at the same time as, or because of, other changes affecting the chemosensory system. Principally, self-reported "taste loss" is a common finding among chemotherapy patients (e.g., Wickham *et al.*, 1999; Berteretche *et al.*, 2004; Rehwaldt *et al.*, 2009; Gamper *et al.*, 2012; IJpma *et al.*, 2015; Amézaga *et al.*, 2018). Taste loss in chemotherapy may occur because cytotoxic drugs can injure multiple cell types in the oral cavity, with gustatory neurons, taste receptor cells, and salivary glands potentially all at risk. Given that much of reported 'flavour' derives from retronasal olfaction (e.g., Murphy & Cain, 1980; Rozin, 1982; and see Spence, 2015, for a review), olfactory toxicity may also be a significant factor in the reported 'taste' changes in chemotherapy (e.g., see Bernhardson, Tishelman, & Rutqvist, 2009) (and see Figure 1). This is the background upon which the 'metal mouth' phenomenon somehow develops.

INSERT FIGURE 1 ABOUT HERE

First, chemotherapy causes a widespread peripheral sensory neuropathy, leading to numbness and sensory loss in a 'stocking and glove' distribution in the extremities. Platinates (e.g., cisplatin, oxaliplatin) form platinum-DNA adducts, leading to the apoptosis of sensory neurons (Fischer *et al*., 2001; Ta *et al*., 2006). Platinates, taxanes (e.g., paclitaxel, docetaxel), and vinca alkaloids (e.g., vinblastine, vincristine) impair microtubule homeostasis, suppressing axonal transport, e.g., of neuronal growth factors (Owellen *et al*., 1976; Topp, Tanner & Levine, 2000; Peters *et al.*, 2007; Velasco & Bruna, 2015). If chemotherapy is also significantly toxic to gustatory neurons, this may help to explain why chemotherapy patients are prone to suffering from a loss of oral sensation, including a loss of taste (e.g., Berteretche *et al.*, 2004; Gamper *et al.*, 2012; IJpma *et al.*, 2015).

Second, it has been reported that chemotherapy is toxic to taste receptor cell progenitors (Mukherjee *et al.*, 2013; Mukherjee *et al.*, 2017; Jewkes *et al.*, 2018; Delay *et al.,* 2019). Following bolus administration of the chemotherapeutic agent cyclophosphamide, mice lose the ability to discriminate between tastants (see Figure 2). This is thought to be attributable to altered turnover: mature taste cells are less likely to be replaced if there are fewer progenitors to replace them. Histological examination following cyclophosphamide administration revealed fewer taste papillae, and more disordered papillar structure, including a lack of taste

pores (Mukherjee & Delay, 2011; Mukherjee *et al.*, 2013). Additionally, loss of innervation to the tongue has independently been found to induce taste bud degeneration (Vintschgau & Hönigschmied, 1877; Huang & Lu, 1996; Huang & Lu, 2001; Guagliardo & Hill, 2007).

INSERT FIGURE 2 ABOUT HERE

Third, chemotherapy may be toxic to salivary glands, as patients commonly suffer from oral dryness (Wickham *et al*., 1999; Jensen *et al*., 2003; Cheng, 2007; Rehwaldt *et al*., 2009). Damage to the salivary glands reduces saliva production, meaning less solvent is present in the oral cavity (see Spence, 2011, for a review). Solutes include taste substances which need to access and bind with their receptors on the tongue (as discussed in Doty & Bromley, 2004); loss of saliva can therefore lead to a loss of taste. Loss of saliva might also cause some background perception similar to astringency—which is described as a feeling of puckering, roughing, or dryness in the mouth (e.g., Lee & Lawless, 1991; but see Fleming, Ziegler, & Hayes, 2016). Astringency is commonly perceived alongside tastes/flavours such as bitter and metallic, for example in metals such as iron and copper (Lawless *et al*., 2004; Lim & Lawless, 2005a; Lim & Lawless, 2005b; Stevens *et al*., 2008; Omur-Ozbek & Dietrich, 2011), as well as in strong tea, coffee, and oaked wine (e.g., Guinard, Pangborn, & Lewis, 1986). Taste-modifying proteins such as carbonic anhydrase 6 (CA6) are also present in saliva; and, among other alterations to the salivary proteome, reduced levels of CA6 have been found in chemotherapy patients (Wang *et al.*, 2018a) and in patients with post-coryzal oral sensory loss (Henkin, Martin, & Agarwal, 1999). On a related note, anecdotal evidence suggests that adding novel taste-modifying substances to saliva (e.g., bromelain, miraculin) may be helpful in terms of diminishing metallic flavour percepts in chemotherapy (Wilken & Satiroff, 2012; Harding, 2017).

To surmise: taste loss in chemotherapy patients could be due to a mixture of off-target toxicities. Nerve cells, taste cells, and salivary glands are damaged. This may be compounded by damage to the flavour-forming tissues of the olfactory system (e.g., Bernhardson, Tishelman, & Rutqvist, 2009). Surrounding this injury are the reactive oxygen species (ROS) generated by chemotherapy, which are known to be cytotoxic (see Yang *et al.*, 2018, for a review); and an altered oral inflammatory state, which there is evidence to suggest may be linked to taste changes. Briefly, TUNEL and cleaved caspase-3 assays indicate that cyclophosphamide-induced taste cell death in mice is necrotic (Mukherjee & Delay, 2011). Inflammation would also incur neuronal death (e.g., Ye *et al*., 2013); and, in an LPS-based experimental model of

inflammation, destruction of proliferating cells aggravated taste cell loss (Cohn *et al*., 2010) just like in chemotherapy. This may be linked to the upregulation of interferons—harbingers of taste cell death (Wang *et al*., 2007). Other inflammatory cytokines such as TNF (tumour necrosis factor) may also distort taste sensations; for example, TNF -/- mice are less sensitive to the bitter taste substance quinine (Feng *et al.*, 2015).

Finally, and importantly, there is immense variability in chemotherapy patients' symptom reports: while some report barely any change in taste, others experience debilitating taste loss and/or metallic sensations. To the best of our knowledge, no association with any particular chemotherapy regime has yet been identified (Amézaga *et al.*, 2018), although the addition of anti-emetics has been found to increase the likelihood of any self-reported taste change (Nolden *et al.*, 2019a). Variability in symptom reports also seems likely to be influenced by inter-personal variance in human taste capacity. Whether PROP 'supertasters' (Bartoshuk, 2000) or other chemosensory variants in the population (e.g., Green & Hayes, 2003; Green & George, 2004; Xu *et al.*, 2007; Allen, McGeary, & Hayes, 2014) report taste alterations more often, and whether taste bud density is correlated with the degree of taste change, are interesting research questions for the future.

Chemotherapy is toxic to a range of sensory structures, and somehow in a subset of individuals the aversive "metallic" percept arises. We will now present the evidence for a series of theoretical explanations for this that warrant future research attention.

The "tinnitus of taste"?

It is currently uncertain whether 'metallic' is a modality of taste. Metals in the mouth may form a miniature Voltaic pile, generating electric current and often a 'metallic' sensation (Sulzer, 1762, p. 82). Modern-day batteries can achieve a similar effect (Lawless *et al*., 2005; McClure & Lawless, 2007; Stevens *et al*., 2008) which could be partly due to metal ions traversing the epithelium of the tongue by ionophoresis. Indeed, the strength of reported 'metallic' sensation evoked by solid metal spoons correlates moderately ($R^2 = 0.33$) with the anodicity of the metal (Laughlin *et al*., 2011).

Taste receptors on the tongue such as T1R3 might bind the metal ions. Broadly-speaking, three populations of T1R-expressing taste receptor cells exist on the murine tongue: T1R1/T1R3 expressing (umami) taste receptor cells; T1R2/T1R3 expressing (sweet) taste receptor cells; and a hitherto-unexplained population of taste receptor cells expressing T1R3 alone (Nelson *et*

197 *al.*, 2001). In T1R3 -/- mice, hedonic responses to metallic (e.g., iron and zinc) solutions are
198 muted (see Figure 3). Furthermore, wild-type mice will drink these metal solutions copiously
199 (Riera *et al.*, 2009a), suggesting that T1R3 agonism might produce a pleasurable metallic
200 sensation in mice, although which taste receptor cell population(s) are responsible for this is
201 not clear. T1R3 has also been characterised separately in the more aversive sensation induced
202 by calcium salts (Tordoff *et al*., 2012). Finally, metal ions have also been found to ligate the
203 bitter taste receptor T2R7 (Wang *et al.*, 2019).

204 INSERT FIGURE 3 ABOUT HERE

205 'Metallic' sensations have also been reported in human participants when several different taste
206 modalities are stimulated synchronously; e.g., during direct electrical stimulation of the chorda
207 tympani (Frenckner & Preber, 1954), and following generalised *damage* to the chorda tympani,
208 for example following ear surgery (Rice, 1963; Bull, 1965; Mahendran, Hogg, & Robinson,
209 2005; Galindo *et al*., 2009). Following nerve damage in the auditory system, there may be no
210 reduction in auditory cortex activity, suggesting that compensatory amplification has occurred
211 (as reviewed by Roberts, 2018). Both noise-evoked and spontaneous activity can be amplified.
212 Amplification of spontaneous activity in the auditory nerve may be experienced by patients as
213 tinnitus ('phantom sound'). Tinnitus (Miaskowski *et al.*, 2018) and other phantoms and
214 distortions (e.g., paraesthesias) have also been reported as side-effects of chemotherapy.
215 Speculatively, chemotherapy-induced nerve damage in the gustatory system might lead to
216 global, synchronous amplification in the chorda tympani experienced as a 'metallic' sensation.
217 One outstanding research question here concerns whether chemotherapy patients experiencing
218 'metal mouth' exhibit altered gustatory cortex activity (e.g., on fMRI) compared to those with
219 no reported oral sensory change. However, a normal representation of metallic on "taste maps"
220 in the gustatory cortex (e.g., Chen *et al.*, 2011; Chikazoe *et al.*, 2019) has not been established.

221 There is limited evidence from studies on human participants undergoing chorda tympani
222 anaesthesia. Here, despite profound local sensory loss, 'sip and spit' testing has revealed little
223 or no loss of whole-mouth taste intensity (see Figure 4) (Ostrom *et al*., 1985; Catalanotto *et al*.,
224 1993; Lehman *et al*., 1995; Yanagisawa *et al*., 1998), suggesting that oral sensory loss can
225 sometimes elicit a compensatory amplification that is somewhat similar to tinnitus.
226 Furthermore, some human participants in these experiments reported experiencing phantom
227 sensations, including 'metallic' phantoms (Yanasigawa *et al.*, 1998), although other taste
228 phantoms (e.g., sweet phantoms) were also reported. Notably, in contrast to chemotherapy,

phantoms under chorda tympani anaesthesia are frequently positively valenced, indicating that chorda tympani anaesthesia is an imperfect model of taste change in chemotherapy. In summary, while something akin to a "tinnitus of taste" model of 'metal mouth' is theoretically conceivable, it is unclear precisely how it would work in practice and, to the best of our knowledge, it has never been investigated.

Sparing the posterior tongue

It is unclear whether the length-dependence of chemotherapy-induced neurotoxicity in the somatosensory system applies to the chorda tympani, with its tortuous length through the petrous part of the temporal bone; but there is evidence that the pattern of gustotoxicity on the tongue roughly follows the distribution of the chorda tympani, with taste receptor cells on the anterior portion of the tongue potentially worst-affected by cyclophosphamide. After cyclophosphamide is injected into mice, anterior (fungiform) papillae are diminished faster, such that type II ($PLC\beta2^{+}$) taste cells tend to die sooner after cyclophosphamide injection if situated more anteriorly on the tongue (see Figure 5) (Mukherjee & Delay, 2011; Mukherjee *et al*., 2013; Mukherjee *et al*., 2017). Because the posterior part of the tongue is disproportionately dedicated to bitter taste (e.g., Adler *et al.*, 2000; Matsunami, Montmayeur, & Buck, 2000; Voigt *et al.*, 2012; Feeney & Hayes, 2014), this suggests that bitter taste faculties might be preferentially preserved under chemotherapy. Not only is hypersensitivity to bitter frequently reported by chemotherapy patients, it is well-correlated with the prevalence of metal mouth as well (IJpma *et al.*, 2017). Recently, solutions of metal salts—including zinc and copper—have been found to ligate the bitter taste receptor T2R7 when expressed in briefly-transfected HEK cells (Wang *et al.*, 2019). This suggests that part of the T2R repertoire is responsive to metals, which may explain some of the overlap between bitter taste and the metallic sensation, which are commonly reported together (e.g., Bromberger & Percival, 2007, p.139). Another bitter taste receptor, T2R5, is thought to be slightly upregulated in chemotherapy patients, especially in those who report phantom sensations (see Figure 6) (Tsutsumi *et al.*, 2016), but to the best of our knowledge, whether T2R7 is upregulated/sensitised in chemotherapy has never been tested in this way. This is worthy of further investigation.

INSERT FIGURE 6 ABOUT HERE

From studies of chorda tympani anaesthesia, participants also reported mildly increased sensitivity to bitter (Lehman *et al*., 1995; Yanagisawa *et al*., 1998). "Cross-talk" between the chorda tympani and glossopharyngeal nerves (see Figure 1) (reviewed in Bartoshuk *et al*., 2005; Snyder & Bartoshuk, 2016) is one suggested mechanism: attenuated signals in the chorda tympani produce a compensatory over-amplification of signals in the glossopharyngeal nerve (a so-called "release-of-inhibition"). The same "release-of-inhibition" might apply to pain signals in the trigeminal nerve (Tie *et al.*, 1999). Multi-dimensional scaling analyses suggest that bitterness and trigeminality are associated with the metallic sensation, being in themselves corollaries of electrical stimulation of the tongue (see Stevens *et al.*, 2008; and also McClure & Lawless, 2007). If cytotoxicity preferentially affects the anterior tongue, "release-of-inhibition" of the posterior tongue may contribute to bitter sensitivity and metal mouth. An outstanding research question is whether there might be any benefit from some form of posterior tongue anaesthesia. Further investigation is required.

A direct effect of the drug?

Many drugs taste foul or bitter (cf. Wan, Woods, Velasco, Salgado-Montejo, & Spence, 2015). Pill formulations are designed to mask this at first-pass, but some compounds evoke 'tastes' when given intravenously (i.v.)—a phenomenon known as 'intravascular taste'. For example, orally ingested saccharin tastes sweet; and human participants seem to experience a similar sweet taste in the oral cavity when saccharin is injected i.v. (Fishberg, Hitzig, & King, 1933). This may be for a number of reasons: for example, saccharin could permeate into saliva; it could pass between tight junctions in taste epithelium; or it could interact with taste receptor cells via the basolateral surface (Schiffman, 2015). This 'intravascular taste' effect with saccharin was recently re-examined, over 80 years after the original experiment, using molecular kinetic analysis (Choi, Lee, & Yun, 2015). By calculating time delays, the authors elegantly concluded that i.v. saccharin probably traverses the tight junctions to enter the oral cavity, eventually eliciting its 'intravascular taste' by the same mechanism (T1R2-T1R3 agonism) as this taste sensation is elicited following oral administration. However, for other taste substances, a different mechanism of 'intravascular taste' may apply. L-arginine—bitter when taken orally (Schiffman, Sennewald, & Gagnon, 1981)—reportedly elicits a metallic sensation in the oral cavity when injected i.v. (Veldhuis *et al*., 2006; Schiffman, 2015), for reasons which remain unclear. For drugs such as amiodarone which elicit metallic sensations, and perhaps for some

chemotherapy agents, unknown taste mechanisms which permit intravascular taste may be at play.

TRPV1 and metals

Nerve endings in skin, and trigeminal nerve endings in the oral mucosa, including on the epithelial surface of the tongue, express TRPV1. TRPV1 is polymodal, responding to pain, temperature, acid, alcohol, and various compounds found in spices, e.g., capsaicin, piperine, and eugenol (see Boonen, Startek, & Talavera, 2017, for a review).

When humans perceive 'metallic' in the mouth, reports occasionally include words like 'burning', 'tingling', 'sharp', or 'not a taste' (Lawless *et al*., 2004; Lubran *et al*., 2005; Lim & Lawless, 2005a). Indeed, there is evidence to suggest metallic transduction could be partly chemesthetic. Artificial sweeteners (e.g., saccharin, acesulfame-K) can be aversive at high concentrations, with bitter and metallic among other sensory qualities reported (Helgren, Lynch, & Kirchmeyer, 1955; Schiffman *et al*., 1995). The bitterness seems to be due to ligation of T2Rs (Kuhn *et al*., 2004), but other aversive components, such as metallic, could be encoded separately. Briefly-transfected HEK cells were used to evaluate bitter taste substances, metallic compounds, and artificial sweeteners and investigate whether they could signal via the polymodal receptor TRPV1. Metallic compounds and artificial sweeteners both activated TRPV1, whereas bitter taste substances did not (Riera *et al*., 2007). This potentially isolates the metallic sensory elements of artificial sweeteners. In behavioural studies, TRPV1 knockout mice were also less averse to artificial sweeteners (Riera *et al*., 2008) and metallic compounds (Riera *et al*., 2009a)—although the effect sizes were small. If metallic compounds are true chemesthetic ligands, there is probably more to the metallic sensation than the 'burn' of TRPV1. Chemesthetic compounds often ligate a profile of different receptors; for example, hydroxy-α-sanshool (from Sichuan peppers) ligates TRPV1, TRPA1, and chemesthetic K^+ channels, which creates a 'tingling' sensation (Bautista *et al*., 2008; Riera *et al*., 2009b; Cometto-Muñiz & Simons, 2015; and see Boonen, Startek, & Talavera, 2017).

Importantly, there is evidence to suggest TRPV1 may be sensitised in chemotherapy. Not only does oxidative stress sensitise TRPV1 (Chuang & Lim, 2009), but at least three chemotherapy drugs—oxaliplatin, paclitaxel, and vincristine—have been found to sensitise TRPV1, markedly heightening capsaicin responses in dorsal root ganglia (see Figure 7) (Anand, Otto, & Anand,

2010; Li *et al*., 2015; Wang *et al*., 2018b). There may be a link to inflammatory activation via interplay with TLR4 (Li *et al.*, 2015) and TNF-α (Wang *et al.*, 2018b). Researchers have not—to the best of our knowledge—investigated whether TRPV1 sensitisation also occurs in the oral cavity during chemotherapy. Chemotherapy patients may report burning oral pain, which is often ascribed to hyposalivation or *Candida* (e.g., Grushka, Epstein, & Gorsky, 2002; Harding, 2017). However, this could also conceivably be a symptom of chemotherapy-induced sensory neuropathy involving TRPV1. Outside the context of chemotherapy, burning oral pain caused by nerve damage (Bartoshuk *et al*., 1999; Lauria *et al*., 2005; Nasri-Heir *et al*., 2011; Jääskeläinen, 2018) is associated with TRPV1 over-expression and bitter-metallic orosensory experiences (Yilmaz *et al*., 2007; Borsani *et al*., 2014). If sensitisation of TRPV1 and/or other chemesthetic receptors is mechanistically important in metal mouth, the design and approval of suitable antagonists could be a possible future supportive therapy for further investigation.

INSERT FIGURE 7 ABOUT HERE

A role for retronasal perception?

Retronasal olfaction (see Figure 8a) occurs when volatiles in the oral cavity pass through the nasopharynx to interact with the olfactory epithelium on the roof of the nasal cavity. This sensory experience is commonly misattributed to the mouth and experienced as "taste" (Murphy & Cain, 1980; Rozin, 1982; Spence, 2015). Nose-clamping experiments with human participants aim to separate retronasal olfactory elements of the flavour experience from taste. According to the logic of this kind of study, in the 'nose unclamped' condition, oral and retronasal elements are both experienced; whereas, with nose clamped, only oral elements are experienced.

INSERT FIGURE 8 ABOUT HERE

Importantly, metals reported as 'metallic' with the nose unclamped can still be sensed in the mouth with the nose clamped (Zacarias *et al*., 2001; Lawless *et al*., 2004; Lawless *et al*., 2005; Lim & Lawless, 2005b; Epke, McClure & Lawless, 2009; Laughlin *et al*., 2011; Skinner *et al*., 2017) strongly suggesting an important oral component to metallic perception. However, especially at low concentrations, retronasal involvement can be particularly crucial: with the nose unclamped, so that retronasal volatiles can enter, participants are often markedly *more*

352 *sensitive* at detecting 'metallic' metals (Hettinger, Myers, & Frank, 1990; Lawless *et al*., 2004;
353 Lawless *et al*., 2005; Lim & Lawless, 2005a; Epke, McClure, & Lawless, 2009; Omur-Ozbek
354 & Dietrich, 2011; Skinner *et al*., 2017).

355 Metal ions themselves are thought to be insufficiently volatile to travel up the nasopharynx (but
356 see Lubran *et al*., 2005; and Skinner *et al*., 2017). So how is the 'metallic' sensation conveyed
357 to the olfactory epithelium? In the dairy industry, 'metallic' volatiles such as 1-octen-3-one (see
358 Figure 8b; at top) were first identified as lipid oxidation products isolated from oxidised
359 butterfat (Stark & Forss, 1962). 1-octen-3-one was later found to be produced from the
360 oxidation of cell membrane lipids such as linoleic acid (Tressl, Bahri, & Engel, 1982; Ullrich
361 & Grosch, 1987). Interestingly, 1-octen-3-one has also been identified as a putative lipid
362 oxidation product from scallops bathed in Fe^{2+}-containing red wine (Tamura *et al.*, 2009;
363 discussed in Spence, Wang, & Youssef, 2017), and as a major contributing volatile to the
364 reported "metallic" flavour in chopped liver (Im, Hayakura, & Kurata, 2004).

365 1-octen-3-one is also formed when metals (iron and copper) are placed on human skin
366 (Glindemann *et al.*, 2006) (see Figure 8c), presumably as a product of the metal-catalysed
367 oxidation of lipids on the skin. Intriguingly, the effect could not be immediately replicated on
368 the same skin patches, suggesting a finite pool of oxidisable lipid on the skin (Glindemann *et*
369 *al*., 2006). Lipid oxidation has also been observed when metals are placed in the oral cavity
370 (Mirlohi, Dietrich, & Duncan, 2011; Omur-Ozbek *et al*., 2012). However, the thiobarbituric
371 acid reactive substances (TBARS) test used could not specifically identify 1-octen-3-one as a
372 metal-catalysed lipid oxidation product here.

373 Theoretically, chemotherapy-induced oxidative stress (Yang *et al*., 2018) could lead to
374 increased intra-oral lipid oxidation, although, again, it is not clear how this profile of lipid
375 oxidation products might be sensorially perceived. It also turns out that the degree of salivary
376 lipid oxidation in cancer patients is a poor predictor of oral sensory change (Mirlohi *et al*.,
377 2015); and again, the TBARS method used cannot discern specific changes in the production
378 of 'metallic' volatiles. In summary, it therefore currently remains unclear whether any
379 significant over-production of 1-octen-3-one and/or other 'metallic' volatiles can occur in
380 chemotherapy.

381 Independently of increased oxidative stress, it is conceivable that 'metallic' volatiles might be
382 produced in chemotherapy patients due to increased traces of blood in the oral cavity in the

context of mucositis, with the iron in haemoglobin able to catalyse lipid oxidation (Glindemann *et al.*, 2006; and see Im, Hayakura, & Kurata, 2004). Alternatively, due to a combination of hyposalivation and immunosuppression, commensals such as *Candida* can overgrow in the oral cavity during chemotherapy (Lalla *et al.*, 2010), and might in theory produce 'metallic' volatiles. 1-octen-3-one can be detected at concentrations as low as 7 ng/L. At these very low concentrations, 1-octen-3-one is not described as "metallic"; instead it is "earthy" or "mushroomy" (Stark & Forss, 1962; Pyysalo, 1976). Indeed, 1-octen-3-one has been identified as a metabolite in various species of mushrooms (Pyysalo, 1976; Tressl, Bahri, & Engel, 1982; Cho *et al*., 2007; Xu *et al.*, 2019) and fungal infections (Darriet *et al*., 2002; la Guerche *et al*., 2006). However, no *Candida* volatile screen has to the best of our knowledge positively identified 1-octen-3-one (negative results include Hertel *et al*., 2016). Further investigation into supportive therapies for metal mouth could focus on repairing the oral mucosa, treating commensal overgrowth, or reducing local oxidative stress.

Finally, and importantly, chemotherapy patients report 'metal mouth', not 'metal nose'. Retronasal olfactory stimuli tend to be perceived as local to the nose *unless* there is also a congruent stimulus present in the oral cavity which can be integrated into a flavour percept (Lim & Johnson, 2011; Lim & Johnson, 2012; Spence, 2016). For example, trace levels of iron and copper in water produce bitterness and astringency in participants with noses clamped. However, with noses unclamped, retronasally-experienced odours do seem to provide congruence, and iron and copper are experienced as 'metallic' (Dietrich, 2009; Omur-Ozbek & Dietrich, 2011).

Conclusions

In conclusion, the purpose of this article has been to provide a much-needed perspective on the origin of the mysterious and under-researched phenomenon of 'metal mouth' as a side-effect of cancer chemotherapy. Although we are necessarily limited in the strength of the conclusions that we can draw due to the lack of research that has been conducted in this area, there remain some compelling theories which we would commend to readers' attention for further investigation in the future.

While a role for retronasal olfaction in metallic perception is well-established (e.g., Lawless *et al*., 2005; Omur-Ozbek & Dietrich, 2011; Skinner *et al*., 2017), metals can also be

independently perceived in the oral cavity (e.g., Zacarias *et al*., 2001; Lawless *et al*., 2005; Laughlin *et al*., 2011; Skinner *et al*., 2017) perhaps as a result of the activation of taste receptor cells or trigeminal nerve endings. There is evidence to suggest metallic compounds can activate T1R3, T2R7, and TRPV1 (Riera *et al.*, 2007; Riera *et al.*, 2009a; Wang *et al.*, 2019).

Metal mouth is among many sensory distortions and phantoms that are associated with cytotoxic chemotherapy drugs (e.g., Bernhardson, Tishelman, & Rutqvist, 2009; Miaskowski *et al*., 2018) which are toxic to nerves (e.g., Peters *et al*., 2007), salivary glands (e.g., Rehwaldt *et al*., 2009), and taste epithelium (e.g., Mukherjee & Delay, 2011). Selective toxicity to the anterior tongue (e.g., Mukherjee *et al.*, 2013) could lead to "release-of-inhibition" (see Snyder & Bartoshuk, 2016); and, perhaps coupled with over-activation of T2Rs (Tsutsumi *et al.*, 2016; Wang *et al.*, 2019), this could help to explain phantoms and hypersensitivity to bitter taste associated with metal mouth (IJpma *et al.*, 2017; but see Yanagisawa *et al.*, 1998). Chemotherapy-induced peripheral sensory neuropathy is linked to the sensitisation of TRPV1 (e.g., Wang *et al*., 2018b) and TRPV1 is also overexpressed following nerve damage in the oral cavity (e.g., Yilmaz *et al.*, 2007). Finally, it has been suggested that metal mouth can be explained by the retronasal activation of olfactory epithelium (e.g., Omur-Ozbek *et al*., 2012), perhaps due to an intra-oral over-production of metallic volatiles, although a source for these metallic volatiles in chemotherapy has yet to be identified (e.g., Mirlohi *et al*., 2015), and it is not clear which congruent stimulus (Lim & Johnson, 2011; Lim & Johnson, 2012) would localise this metallic percept to the mouth. Further investigation is required, both into the aetiology of metal mouth and into possible supportive therapies.

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Figure Legends

Figure 1. Simplified illustration of the contribution of taste to flavour. Key elements are emphasised: namely, the cross-talk between the chorda tympani and the glossopharyngeal nerve, which may involve reciprocal inhibition; the presence of broadly-discrete clusters of taste buds on the tongue, which have separate innervation; and the integration of olfactory inputs into flavour perception. Note that several of these flavour-forming structures are affected by the action of cytotoxic drugs.

Figure 2. An example of loss of taste function in chemotherapy. CYP = cyclophosphamide group (injected with bolus on day 0), saline = control. Mice were tested on their ability to discriminate (% successful detection) between umami taste substances monosodium glutamate and IMP, which control mice can discriminate ~90% of the time. The relative failure of mice in the CYP group to discriminate (50% = chance) could be linked to the direct effect of losing taste receptor cells in the umami modality (i.e., a loss of sensitivity); to concomitant nerve damage; or to abnormal modulation of taste receptor cell activity, e.g., by cytokines. This loss of umami taste discrimination following a cyclophosphamide bolus appears to be biphasic, probably because of the different life expectancies of taste receptor cell populations in the tongue. S^P = punisher for failure to discriminate. [Figure reproduced from Mukherjee & Delay, 2011, with permission from Elsevier.]

Figure 3. T1R3 -/- mice exhibit no significant preference for concentrations of metal sulphate solutions which wild-type mice find hedonically appealing (when compared to water). Preference ratios from two-bottle tests where metal sulphate solution was presented in the cage alongside water. Preference ratio = volume of metal sulphate solution consumed ÷ (total volume of metal sulphate solution + volume of water consumed). Top: iron sulphate solution; bottom: zinc sulphate solution. [Reproduced from Riera *et al.*, 2009a, with permission from the Society for Neuroscience via Copyright Clearance Center.]

Figure 4. In unilateral chorda tympani anaesthesia, despite local sensory loss on the ipsilateral side of the tongue (Front of the Tongue, Right), there is no loss of reported whole-mouth taste intensity of the tastants sodium chloride (NaCl, salty), sucrose (Suc, sweet), and citric acid (CA, sour); and there is an increase in reported whole-mouth taste intensity of quinine hydrochloride (QHCl, bitter). [Reproduced from Lehman *et al.*, 1995, with permission from Elsevier.]

Figure 5. PLCβ2^{+} (type II) taste receptor cells in fungiform papillae on the anterior tongue (left) are diminished faster following administration of cyclophosphamide bolus (on day 0) than PLCβ2^{+} (type II) taste receptor cells in circumvallate papillae on the posterior tongue (right). CYP = cyclophosphamide group; AMF/CYP = cyclophosphamide group treated with cytoprotectant, amifostine. [Reproduced from Mukherjee *et al.*, 2013, under CC-BY license.]

Figure 6. A. Zinc sulphate solution activates the bitter taste receptor T2R7 in briefly-transfected HEK cells. RFU = relative fluorescence units, fluo-4 Ca^{2+} indicator used. Black trace: HEK cell transfected with T2R7; green-grey trace: mock-transfected HEK cell. [Figure reproduced from Wang *et al*., 2019, under CC-BY license.] B. Upregulation of another bitter taste receptor, T2R5, in the lingual epithelia of chemotherapy patients only occurs to a significant extent if phantom sensations are also present. [Reproduced from Tsutsumi *et al.*, 2016, with permission from John Wiley & Sons via Copyright Clearance Center.]

Figure 7. Upregulation of TRPV1 shown by Western blot (left), and sensitisation of TRPV1 shown by patch-clamp (right), in dorsal root ganglia from rats treated with vincristine. Similar data exist for oxaliplatin and paclitaxel. [Reproduced from Wang *et al*., 2018b, with permission from Spandidos Publications.]

Figure 8. A. Simplified illustration of the difference between orthonasal and retronasal olfaction. [Reproduced from Dietrich, 2009, with permission from IWA Publishing.] We can only retronasally experience olfactory stimuli that are already present in the oral cavity—and they can only be mislocalised as "tastes" if a congruent sensory stimulus is also present in the

oral cavity (see Spence, 2016, for a review). B. Skeletal formulae of some 'metallic' volatiles. From top: 1-octen-3-one, 1-nonen-3-one, (Z)-1,5-octadien-3-one. Humans are exquisitely sensitive to 1-octen-3-one, which remains odorous at a concentration of 7 ng/L—although the character of this odour changes from 'metallic' to 'mushroom' at low concentrations. [Structures drawn with PubChem Sketcher.] C. Formation of 1-octen-3-one on GC-MS when metal is placed on human skin. Despite being a small peak, because it is detectable at such low concentrations, 1-octen-3-one is the most significant contributor to the 'metallic' odour out of all of the volatiles identified. [Reproduced from Glindemann *et al.*, 2006, with permission from John Wiley & Sons via Copyright Clearance Center.]

Table 1. Studies reporting the prevalence of 'metal mouth' sensations in chemotherapy patients, in chronological order. Updated from the list of studies up to 2014 provided by IJpma *et al.*, 2015.