Current Nutrition Reports (2021) 10:137–145
https://doi.org/10.1007/s13668-021-00355-3

NUTRITION AND THE BRAIN (J NASSER, SECTION EDITOR)

# To Detect and Reject, Parallel Roles for Taste and Immunity

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Accepted: 23 March 2021 / Published online: 22 April 2021


## Abstract

**Purpose of Review** From single cells to entire organisms, biological entities are in constant communication with their surroundings, deciding what to 'allow' in, and what to reject. In very different ways, the immune and taste systems both fulfill this function, with growing evidence suggesting a relationship between the two, through shared signaling pathways, receptors, and feedback loops. The purpose of this review was to explore recent reports on taste and immunity in model animals and in humans to explore our understanding of the interplay between these systems.

**Recent Findings** Acute infections in the upper airway, as with SARS-CoV-2, are associated with a proinflammatory state, and blunted taste perception. Further, recent findings highlight taste receptors working as immune sentinels throughout the body. Work in humans and mice also points to inflammation from obesity impacting taste, altering taste bud abundance and composition.

**Summary** There is accumulating evidence that taste cells, and particularly their receptors, play a role in airway and gut immunity, responsive to invading organisms. Inflammation itself may further act on taste buds and other taste receptor expressing cells throughout the body as a form of homeostatic control.

**Keywords** Taste · Inflammation · Immunity · Obesity

## Introduction

Taste is fundamentally linked to quality of life, and is vital in determining food choice. However, as well as to assay the appeal of foods with appetitive characteristics, the taste system chemically interrogates the food we eat, serving as a gatekeeper, protecting against the ingestion of aversive, unpalatable items that may cause harm if taken into the body. The immune system serves an analogous function, detecting things that are harmful, or that bear the molecular signals of those that have been harmful in the past, acutely activating against systemic insult as a first line of defense. In the time necessary for an adaptive immune response to generate, a pathogen may have grown to a problematic degree within the host, and therefore the innate immune response gives an "always on" protection to the body from novel pathogens it may be initially naive to. The innate immune response utilizes an array of cells, signaling factors and proteins to isolate, destroy and recycle potential pathogens before they can reproduce to the point where they may become harmful to the host. Without an index of specific pathogens to identify, the innate immune response instead relies on detecting common molecules which are absent in the host, but which are often signs of a pathogenic entity, the classical example being Lipopolysaccharides, molecules commonly found in the external membranes of Gram-negative bacteria. Upon detection, the innate immune system responds to neutralize a perceived threat with both phagocytosis, whereby a potential intruder is engulfed and ingested, and with inflammation.

As the basic roles of immunity and taste share some overlap in function, it is unsurprising then that recent evidence has begun to suggest that these systems may interact, and further may influence one another. Most visibly in the past year during the Covid-19 pandemic, infection with the novel coronavirus was strongly and publicly associated with anosmia, a loss of smell [1], in a manner that may correlate with an activated inflammatory response [2], as well as with ageusia, a loss of taste, and further loss of oral perception of irritants [3••]. Taste cells and their canonical signaling cascades are

This article is part of the Topical Collection on *Nutrition and the Brain*

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commonly implicated in auto and hyperimmune diseases. Many genes associated with the innate immune response are over-expressed in taste cells, particularly in those isolated from taste cells bearing the molecular signals of type II taste cells [4], the cells responsible for sweet, umami and bitter taste detection. In the taste buds of humans, inflammation and innate immune-associated genes are readily up-regulated in obese compared to lean individuals [5••]. Being overweight or obese (a condition affecting over 65% of adults in the USA), is associated with chronic low-grade inflammation, and is linked to alterations in taste or food intake patterns, usually promoting overconsumption, and correlating with a loss of taste function. Taken together, evidence points toward a feedback relationship between the immune and taste systems that may have implications for how the body functions to keep us safe from pathogens, and for our metabolic health in general.

In this review, we will concentrate on recent findings (primarily those from the past 5 years) regarding immunity, inflammation, and taste to provide a snapshot of our current understanding of how these systems interact, and highlight further interesting questions that future work may explore.

## Search strategy and selection criteria

PubMed and Google Scholar were used to search for primary research articles, over the previous 5 full years from 2016 to 2020, with a small number of important articles from earlier than this also included for context. Search terms included "taste", "inflammation", "immunity", "autoimmune", "obesity", "cancer", and various combinations thereof. Summaries and reviews were largely excluded to concentrate on most recent primary literature from the lab or clinic. Recent studies in non-human animals are highlighted in Table 1, with studies in human subjects in Table 2.

## Molecular markers of inflammation

Inflammation as a term encompasses the activation of the immune system toward an insult. This is characterized on the macroscale by an increase in blood flow leading to redness, swelling, and an increase in temperature, along with pain and potentially a temporary loss of function [18], and on the cellular scale by the recruitment of neutrophils, macrophages, and monocytes, as well as proinflammatory cytokines like Tumor Necrosis Factor alpha (TNFα) [19] and Interluekin-6 (IL-6) [20], other markers of inflammation like C-Reactive Protein (CRP) [21] and chemokines like Monocyte Chemoattractant Protein-1 (MCP-1) [20]. This contrasts with the more specific actions of the adaptive immune system acting post antigen presentation via B or T cells, to an already familiar threat.

While, in many cases, these acute phase effectors resolve after insult, a chronic low-grade inflammation, or metaflammation [22], has been observed in overnutrition and obesity [23]. Overfeeding also leads to hyperinsulemia and hyperleptinemia [24], as resistance to the effects of insulin or leptin necessitates their overproduction. Evidence points to proinflammatory cytokines directly acting on the insulin [25] receptor, and leptin receptors (among other mechanisms of leptin resistance [26, 27]) to affect this change. Interestingly, many proinflammatory signaling factors associated with inflammation also have their cogent receptors expressed in taste buds [28–30], proffering a potential mechanism for their up- or down-regulation being associated with a modulation of taste function. TNFα knock out (KO) mice are less sensitive to bitter stimuli than wild type animals [31], and exogenous TNFα seems to blunt sodium taste by inhibiting sodium flux in taste buds [32].

## Bacterial infection

Lipopolysaccharide (LPS), an inducer of acute inflammation of bacterial origin, has been utilized by multiple groups to model the influence of systemic inflammation on the taste system. Exogenous LPS resulted in a reduction in the proliferative capacity of taste buds [33] which are constantly renewing in nature, and altered licking response to NaCl in mice [32, 34], supported by reduced activity in the *chorda tympani* nerve which takes taste information from the anterior tongue to the brain, in response to various taste stimuli [34••]. Serum-LPS is also elevated in mice experiencing systemic inflammation through consuming a high-fat diet (HFD) [11••]. In one intriguing study, the bitter tastant (of recent infamy), chloroquine, was found to exhibit protective effects on pre-term birth in mice, when induced through LPS injections (inflammation is a key risk factor for pre-term labor) [35]. Protective effects were much weaker in animals lacking the G-protein alpha-subunit Gustducin (originally thought to be taste-specific, although now associated with many chemosensory cells throughout the body), suggesting that protective effects were mediated in a manner analogous to taste signaling, via bitter receptors which were found expressed in myometrial cells. Interestingly, the primary receptor for LPS, TLR4 [30], is also expressed in taste buds, whereby taste preference is altered in mice deficient in TLR4, with KO mice displaying a reduced preference for sugars, lipids, and umami [36], further suggesting that an innate inflammatory response may alter taste function. Taken together with earlier work, this suggests a dual function for the LPS/TLR4 pathway; (1) as a sensor of inflammation which can damage taste buds, and (2)

**Table 1** Studies in non-human models of inflammation and their consequences for taste from 2016 to 2020

| Reference | Study objective | Study Design | Model | Measures | Results | Conclusions |
|---|---|---|---|---|---|---|
| Ahart et al. (2020) [6••] | Determine whether HFD or obesity itself induced taste deficits | Mice on HFD or Chow with or without Captopril (CAP) in water for 6 weeks | C57BL/6 mice Diet Induced Obesity (DIO) | Sucrose licking, calcium imaging of taste cells, taste gene expression. | HFD but not Obesity reduced licking of sucrose.<br>Diet independently inhibited TRC activity.<br>No decrease of TBs in HFD. Decrease in PLCB2 | Both diet itself *and* obesity independently impact taste. |
| Kaufman et al (2020) [7] | Taste stem cell associated markers were measure in obese and lean mice | Mice on control diets or HFD for 8 weeks. | C57BL/6J Male mice, circumvallate papillae gene expression | qRT-PCR, genes expressed in TBs isolated from CV of mice. | Reduction of expression in HFD-fed mice of markers of proliferation->Ki-67 and β-catenin, and markers of all taste cell types- PLCβ2, KCNQ1, NPTDase2, PKD2L1 | Gene expression of proliferation markers significantly reduced in the TBs of obese mice. |
| Bernard et al. (2019) [8] | Explore fat detection in obese rodents | 1) Mice on chronic HFD and 2) 4 week treatment with LPS through osmotic pump to recreate a chronic inflammation. | C57Bl/6 male mice age 8 weeks | Two bottle preference with oil solution, LPS detection, taste gene expression, | DIO mice had a decreased preference for oil. Plasma LPS increased in DIO mice.<br>LPS alone did not change preference for oil.<br>Proinflammatory genes increase in Circumvallate Papillate (CVP) of LPS mice with NFκB a central mediator | Orosensory perception of fat is affected by a fatty diet, but not by a non-diet LPS induced proinflammatory state |
| Bernard et al. (2019) [9••] | Determine whether prebiotic supplementation reverses DIO taste changes in mice | Mice on Chow or HFD alone and supplemented with 10% prebiotic for 12 weeks. | C57 Bl / 6 males. Age 7 weeks to start. | Two bottle taste preference, gustometer, blood draw, gut microbiota | DIO group reduced response to sucrose in two bottle and gustometer. Partially rescued by prebiotic (P).<br>Proglucagon increase in DIO+Probiotic group | Though markers weren't measured, the authors indicate anti-inflammatory effects of prebiotic might partially explain sweet taste rescue |
| Kaufman et al. (2018) [10••] | Investigate association of obesity with taste abundance in mice | Wild type C57, TNFαKO and Sel 1L adipocyte KO fed HFD or Chow. Acute injection of TNFα or vehicle into tongue. | 8-week-old C57 Bl/6, B6.129S-Tnftm1Gkl/J, Sel 1L-/- ,all male | Taste bud and Taste Receptor Cell and taste progenitor cell counting, mRNA of stem cells and taste transduction markers. | Obese mice have elevated TNFα and concomitant taste bud loss. TNFα null mice and obese-resistant mice are protected. Taste progenitor (Ki67+) cells also reduced with bud loss. | Inflammation arising from obesity, associated with adipose tissue reduces the # of taste buds through a reduction in progenitor cells. |
| Djezriri et al. (2018) [11••] | Mediterranean diets high in polyunsaturated fats exert anti-obesity effects. Mechanism explored in mice. | Mice on control diets or HFD with poly unsaturated fat in water or vehicle. | C57BL/6J Female mice on Chow, HFD, or HFD + oleanolic acid (OLA) in water for 16 weeks. | Plasma LPS, Taste Preference, Cytokine mRNA, fatty acid composition of tissue, blood glucose tolerance test. | OLA decreases weight gain of HFD mice, rescues CD36 expression, improves Glucose response, and reduces plasma LPS.<br>Reduces TNFα, IL-1β, and IL-6 vs HFD alone.<br>$Ca^{2+}$ flux to OLA was abolished in HFD but rescued with HFD + OLA mice in a through CD36 independent pathway. | Reduction in bodyweight, pro-inflammatory cytokines, glucose response, and restoration of taste acuity all through addition of OLA to diet. |
| Feng et al. (2018) [12••] | As TRCs have been found in the gut, group investigated whether α-Gustducin has a role in IBD, a gut inflammatory disorder | Induced colitis in either C57Bl/6 or their α-Gust null counterparts. | Animal model of IBD, using dextran sulfate sodium (DSS) to induce inflammation in α-gust-KO mice.<br>M /F both used. 3% DSS in water for 7 days, then mice were euthanized. | Weight, cytokine measures in colon tissue, immunohistochemistry (IHC) | α-Gust null mice had more severe colitis than WT, lost more weight, had higher tissue injury score, more inflammatory cell infiltration in colons plus an increase in TNF and IFN-γ.<br>Decrease in IL-5, IL-13, IL-10 | α-Gust serves a critical role in protecting the colon from inflammation. |
| Sharma et al. (2017) [13••] | GPCRs in Asthma are targets for treatment. As new evidence implicates T2R bitter receptors, which are GPCRS, in inflammatory pathways, bitter taste receptor agonists were tested as asthma treatments. | Mice treated with T2R agonists chloroquine (CQ) or quinine (Q) and challenged with Ovalbumin (OVA) or House Dust Mites (HDM)<br>Used human neutrophils to determine mechanism | Male FVB/N mice 8 weeks old;<br>Injected with OVA Intraperitoneally then challenged with or without agonists.<br>Female BALB/c mice 8 weeks old challenged with HDM.<br>Two models;<br>Prophylactic: pre-treated with agonists coincides with initial HDM challenge | Neutrophil Migration, cytokines (IL-4,5,9,13,17,10), lung mechanics, Bronchoalveolar lavage cell counts (Eosinophils, neutrophils, macrophages, lymphocytes), various IHC staining for mucus accumulation via PAS | **Inflammation:** T2R Agonists reduced induction of IL-4,5,13,17, eotaxin, and keratinocyte chemoattractant. Failed to repress TNFα, IP-10, and RANTES.<br>**Remodeling**: lower collagen deposition and fibronectin expression by taste receptors,.<br>Differential effects in inhibiting matrix metalloproteinases<br>**Mechanism**<br>Dose dependent reduction in immune cell recruitment by Q and CQ. | CQ and Q differentially inhibited most chemokines and cytokines, Q was overall more effective than CQ at suppressing inflammation. |

**Table 1** (continued)

| Reference | Study objective | Study Design | Model | Measures | Results | Conclusions |
|---|---|---|---|---|---|---|
| Howitt et al. (2016) [14••] | Tuft cells, a gut immune cell that can detect parasites, contain taste receptors. Here their downstream signaling pathway is investigated in detail. | WT and *TRPM5*$^{-/-}$ mice challenged with *Tritrichomonas muris* (Tm) in a model of helminth infection. Tuft cells were analyzed by IHC + Intestinal organoids cultured to measure Interleukin production. *Rag2*$^{-/-}$*.Il-2*$^{rγ-/-}$ Mice lacking $T_h2$ and ILC2 cells | WT and *TRPM5*$^{-/-}$ mice, DCLK1+ (tuft cells), intestinal organoids | Interleukin gene expression<br>Flow cytometry cell counting | Upon infection with Tm, *TRPM5*$^{-/-}$ had reduced IL-25, IL-13, fewer Type2 innate lymphoid cells, and concomitant tuft cell expansion.<br>Additionally, | TRPM5 taste transduction signaling may be used to detect Tm, which excited innate lymphoid type 2 cells (ILC2s), producing IL-13 and thereby promoting their own proliferation |

as an integral part of the sensory transduction pathway, without which taste sensations are altered.

A critical recent finding that will doubtlessly accelerate our understanding of the nexus between innate immunity and taste is that taste organoid cultures are also able to model an inflammatory response such as that in bacterial infiltration in vivo, with rapid induction of TNF and IL-6 observed in these in vitro cultures after stimulation with LPS [37]. These taste organoids also expressed many other classical markers of the immune response, including all members of the NF-κB protein complex (NF-κB1, NF-κB2, RelA, RelB, c-Rel,) and multiple Toll-like receptors, most markedly TLR2, 3, 4, and 5.

## The gastrointestinal tract

Several autoimmune diseases are also linked to taste dysfunction, notably Sjögren's Syndrome (SS) [38], Inflammatory Bowel Disease (IBD) [39], and Systemic Lupus Erythematosus (SLE) in mice [40]. Each of these diseases impact taste signaling in their own way. For example, in SS, patients experience an infiltration of macrophages, plasma, and T cells into their lacrimal and salivary glands [41]. This leads to a reduction in salivary production, which itself reduces the ability to detect taste compounds, though not necessarily through a direct action on taste cells. In a mouse model of autoimmune disease with a phenotype akin to that of lupus or Sjögren's syndrome, taste buds were smaller, and fewer taste cells regenerated from taste stem cells in the native turnover process the a taste bud relies on to maintain fidelity [42]. In humans with IBD, taste sensitivity was generally blunted versus healthy controls, save for sour taste, which was elevated in IBD. Sour is thought to be transduced through Type III taste cells [43]; however, most of the receptors associated with the immune response that are reported to be present in the taste bud tend to be expressed in Type II cells [29, 44, 45]. In human colonic mucosa, the number of bitter-receptor (T2R38) expressing cells is higher in those who are obese than lean, and is confined to cells seeming to fit an enteroendocrine phenotype [46]. These cells would presumably be responsible for the chemical sensing of luminal contents, with their abundance strongly correlating with BMI in this sample. Interestingly, the stimulation of T2R108 receptors in enteroendocrine cells in the guts of diet-induced obese mice with a bitter extract from hops was linked to GLP-1 release, and an improvement in multiple metabolic measures including fat mass, glucose homeostasis and insulin sensitivity [47].

## Airway immunity

When encountering microbes in the airway, the innate immune response must detect and respond to potentially harmful

invaders, in a manner thought to be partially dependent on the T2R family of bitter receptors (for review see [44]). A recent report suggested that cells in the trachea expressing bitter taste receptors also expressed the tuft cell marker (a chemosensory cell located in the epithelium, linked to type 2 immunity through the taste-linked signaling channel TRPM5 (Transient receptor potential cation channel subfamily M member 5) [14••], DCLK1 (microtubule-linked protein kinase 1), comprising around 4% of epithelial cells [48]. When isolating mRNA from these cells, sequencing revealed RNA for multiple additional taste signaling elements, as well as for multiple cytokines implicated in the immune response.

Interestingly, many of the antibiotics commonly used to treat airway infections (including levofloxacin, tobramycin, and azithromycin) are also capable of activating the T2Rs (T2R1, T2R4, T2R14, and T2R20) present in the airway, validated in an in vitro FLAG tagged HEK cell system [49]. These receptors are expressed in smooth muscle cells within the airway walls, functioning in a manner that seems ancillary to the inflammatory response, to relax smooth muscles and aid in bronchodilation [50]. Using cultured human sinonasal epithelial cells, Lee et al. [51••] were able to demonstrate that solitary chemosensory cells in the airway express the same T1R2/T1R3 receptor heterodimers present in taste buds used for sweet taste detection. While amino acids have a range of tastes, some D-amino acids are able to activate the T1R2/T1R3 receptor, where in the mouth this would correlate to the eliciting of a sweet taste [52]. Lee et al. found that not only do bacterial isolates, for example Staphylococcus, from human airways produce several of such T1R-activating D-amino acids (D-Leucine, D-Isoleucine, D-Phenylalanine), but also D-amino acids taken from these isolates were able to inhibit biofilm formation in a T1R-dependant manner.

## Cancer and its treatment

Cancer, the inflammatory state association with it, and the treatment side-effects thereof are also all associated with changes in taste in humans [53, 54]. In mice, the effects of cyclophosphamide, a common chemotherapeutic agent, are acutely damaging to taste cells, in particular type II and III cells [55]. This loss of taste cells seems to act through apoptosis, and be particularly damaging to the progenitor cells responsible for resupplying the taste bud. When fractionating doses of cyclophosphamide, a practice common in cancer treatment that can alleviate some of the more negative side effects commonly encountered, loss of taste was in fact prolonged, and more severe [56]. As taste loss can discourage eating, leading to broad negative outcomes, and further result in a significant reduction in quality of life, careful consideration should be made of the implications of these findings.

As cancer patients are at risk of cachexia (a wasting disorder characterized by severe extreme weight loss along with loss of muscle and body fat, and marked by a loss of appetite) and its associated morbidity and mortality, a recent study worked to untangle the attribution of each [15]. Counter to the hypothesis that treatment which damages rapidly dividing cells would impact taste cell renewal, the authors found no impact of chemotherapy on taste detection in hospitalized patients. They did find altered taste perception in both the chemotherapy and acute inflammatory group versus healthy controls; however, the marker CRP, and leukocyte counts did not correlate with dysfunction. This suggests that a broader inflammatory state may be affecting both populations. Care should be taken in interpreting these results as the study populations were, by the nature of the study, not standardized.

## Obesity, inflammation and taste

While acute inflammation in the form of infection is well characterized, a chronic low-grade inflammation associated with obesity [57] is a remarkably widespread manifestation of long-term activation of the immune system. In obesity, white adipose tissue (WAT) is broadly remodeled, and is itself a source of cytokines [58], and a harbor for macrophages that promote systemic inflammation [59]. Further, pathologies associated with obesity such as atherosclerosis have an immune component themselves, with associated plaques composed of several types of immune cells, including macrophages and neutrophils [60]. Obesity is associated with lower levels of adiponectin, and higher levels of TNF$\alpha$ [61], IL-6, and C-Reactive Protein (CRP) [62]. IL-6 and CRP are associated with disease complications [63, 64], while TNF$\alpha$ is associated with insulin resistance and hyperleptinemia [65, 66]. One recent study also implicated various signaling elements of taste (T1R2, T1R3, G$\alpha$-Gustducin, phospholipase C-beta 2, and TRPM5 channels) expressed in renal tissues in stimulation of the inflammasome, in a diabetic mouse model, where activation of the inflammasome could further be partially mediated by the sweet taste blocker lactisole [67].

A great deal of studies associate taste changes with obesity, with the preponderance of evidence supporting a reduction taste acuity [7, 68–70], although some work does show the opposite effect [71] or no change at all [72]. Recent work from our own group suggested a reduction in taste bud abundance in both mice [10••] and humans [7] with adiposity, alongside a reduction in expression of various taste-linked signaling elements in mice [7]. The latter result is paralleled in humans in work from Archer et al. [5••], where a pioneering RNA sequencing experiment examined differential expression patterns of obese and lean Caucasian women, from isolated fungiform taste papillae. In fact, 2 of the 3 ontological groupings of genes found to vary significantly between subjects were

**Table 2** Studies with human models of inflammation and their taste consequences from 2016 to 2020

| Reference | Study objective | Study design | Model | Measures | Results | Conclusions |
|---|---|---|---|---|---|---|
| Kaufman et al. (2020) [7] | Investigating changes in human taste bud abundance in increased bodyweight individuals non-invasively. | Taste buds counting from humans enrolled in a longitudinal study designed to measure college weight gain were counted | $n = 49$ (39 F, 10 M) subjects originally aged 17–18.<br>Measurements obtained during freshman year and again 4 years later | Neck circumference measured as a proxy for bodyweight along with BMI, fungiform TBs counted.. | Change in fungiform density inversely correlated with neck circumference. $R = -0.374$, $p = 0.008$ | Although not a direct measure of taste buds per se`, taste papillae were diminished with increasing neck circumference, an accepted measure of adiposity. |
| Schalk et al. (2018) [15] | Investigating the contribution of cancer, its treatment, inflammation resulting from either, and concomitant taste-dysfunction on malnutrition | Measure taste, inflammation and effect of chemotherapy on each in patients with cancer. | 138 patients, mean age 65.2 in three groups.<br>Group 1: 42 patients hospitalized due to cancer undergoing chemotherapy<br>Group 2: 57 patients hospitalized for an acute inflammatory disease without malignancy<br>Group 3: 39 healthy study participants | Sniffin' Sticks for olfaction, recognition taste test for 5 basic tastes.<br>Detection and recognition threshold recorded. | No significant difference between patients with or without chemotherapeutical treatment.<br>Recognition and detection thresholds were significantly different between hospitalized patients and healthy controls.<br>Cancer patients and hospitalized patients with inflammatory disease both exhibited taste dysfunction versus healthy controls.<br>Inflammatory status as measured by CRP and leukocyte count did not directly associated with changes in taste | Inflammation, not chemotherapy, impacted taste function. As specific measures of inflammation did not correlate with taste dysfunction, mechanism is likely mediated through other proinflammatory cytokines (not CRP/leukocytes). |
| Archer et al. (2018) [5] | Determine whether there is a difference in molecular makeup of taste tissue in lean and obese individuals. | RNA transcript analysis of fungiform TB biopsies | Human Female Caucasians, lean ($n = 23$) and obese ($n = 13$) BMI >30 | Fungiform papillae counting, RNA-seq | No difference in papillae count.<br>Highly divergent gene expression: PLCβ2& Sonic Hedge Hog (SHH) ↓in obese vs lean<br>Top ↑pathways associated with immune and inflammatory response.<br>Generally ↓ expression of taste genes in obese, mostly type II. | Evidence in humans that immune and taste gene expression is altered in obese vs lean individuals. |
| Noel et al. (2017) [16] | Investigate relationship between reduced sweet taste function and sweet solution intake | Participants had sweet taste inhibited and performed ad-libitum mixing task to an optimal sweetness level, along with tasting various sweet foods | Repeated session with *Gymnema sylvestre(GS)* to inhibit sweet taste function to varying levels versus blank in 51 participants | gLMS ratings of sweetness with various levels of GS, compared with liking of sweet foods, plus ideal concentration of sugar in beverage from ad lib mixing task. | GS reduced sweet taste significantly vs control. Reduction in intensity perception was associated with an increase in desired sucrose in the ad-libitum mixing task.<br>An incremental 1% reduction in rated sweetness intensity corresponded to a 0.4 g/L increase in desired sucrose. | Weakened sense of sweet taste was associated with an increased desire for sweeter beverages.<br>Taste damage may thus lead to the desire for more energy dense foods. |
| Adappa et al. (2016) [17] | Investigate T2R38 phenotype status on biofilm formation in patients with chronic rhinosinusitis (CRS) | Recruit CRS positive patients with evidence of immune activation, genotype, taste tests, and biofilm assay. | Human subjects >18 yrs (M and F), immune competent CRS patients with evidence of sinonasal inflammation. 59 subjects | 13 point PTC taste test, biofilm formation assay, T2R38 genotyping | PTC taste score correlates with biofilm formation in patients without polyps ($p = 0026$).<br>Increasing PTC taste score was inversely correlated with biofilm formation in nonpolyploid patients. | Increased T2R38 expression in the airway may be associated with a reduction in biofilm formation. |

those associated with the immune response, and with sensory signaling.

Interestingly, in regions of the brain related to energy homeostasis (the hypothalamus and brainstem), both taste receptors (T1R3, T2R116) and taste signaling elements (Gα14, TRPM5) are down-regulated by obesity in mice [73], in a manner which, we might speculate, seems itself homeostatic in nature. Although in an acute model of taste loss panelists tend to select foods of a higher sensory impact, and thus caloric content [16], a large genome-wide association study found limited evidence for an association between taste response and polymorphisms in taste genes, although GNAT3 alleles associated with greater sweet taste response were negatively associated with sugar intake in one sample [74]. Studies of patients undergoing bariatric surgery point toward rapid changes in taste after extreme weight loss [75–77], which may be inflammation-linked, as well as depending on the hormonal remodeling common in such interventions. Further work even implicates dampened CNS reward circuity linked to taste with an increase in obesity in adults [78, 79], which may differ from that seen in children [80].

Taste buds, or more specifically the population of specialized epithelial cells that make them up, are constantly renewed from a population of stem cells, which produce taste progenitor cells that further differentiate into 3 functionally and morphologically distinct taste cells [81], each cell type having a distinct half-life [82], or supporting keratinocytes. This complex and constant state of development requires a finely tuned balance of developmental and transcriptional regulators within the taste bud to ensure the judicious turnover of taste cells within the bud. The recent report by Archer [5••] showed a downregulation of genes expressed in the Type II taste cells responsible for sweet, bitter or umami detection in the fungiform papillae of obese versus lean women, as well as a reduction in expression of sonic hedge-hog (*SHH*), a morphogen vital for taste cell development [83, 84]. Kaufman et al. showed a similar decrease in taste cell developmental markers in obese mice [7], with a concomitant increase in inflammatory markers and fewer taste buds in obese mice from an earlier work [10••].

## Conclusions and future work

Taste perception in humans is sensitive to disease states, including obesity and acute infection. Circulating factors arising from our inflammatory state can also interact with taste cells themselves, their progenitor cells, innervating nerves, and with processing within the brain.

Recent work has made it clear that the taste system is plastic and responds to inflammatory insult, whether acute or chronic, and thus inflammation has a role in taste function and intake which cannot be discounted as we work toward behavioral approaches to treat metabolic diseases. Further, the identification of cells strikingly similar in phenotype to those we think of as taste cells throughout the body, which are seemingly fulfilling an immune sentinel role, highlights further links between immunity and taste. Future work should take advantage of the expanding array of molecular techniques available to study taste cells in vitro, and aim for longitudinal studies of taste and immunity pre- and post-obesity, to further elucidate the complex relationship between our perception of foods, and the consequences of over consumption.

## Declarations

**Conflict of interest** authors do not have any potential conflicts of interest to disclose.

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**concomitant taste dysfunction. Prebiotic rescued sweet taste preference in mice consuming a HFD.**

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