Ecological Sensing Through Taste and Chemosensation Mediates Inflammation: A Biological Anthropological Approach

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ABSTRACT

Ecological sensing and inflammation have evolved to ensure optima between organism survival and reproductive success in different and changing environments. At the molecular level, ecological sensing consists of many types of receptors located in different tissues that orchestrate integrated responses (immune, neuroendocrine systems) to external and internal stimuli. This review describes emerging data on taste and chemosensory receptors, proposing them as broad ecological sensors and providing evidence that taste perception is shaped not only according to sense epitopes from nutrients but also in response to highly diverse external and internal stimuli. We apply a biological anthropological approach to examine how ecological sensing has been shaped by these stimuli through human evolution for complex interkingdom communication between a host and pathological and symbiotic bacteria, focusing on population-specific genetic diversity. We then focus on how these sensory receptors play a major role in inflammatory processes that form the basis of many modern common metabolic diseases such as obesity, type 2 diabetes, and aging. The impacts of human niche construction and cultural evolution in shaping environments are described with emphasis on consequent biological responsiveness. *Adv Nutr* 2020;11:1671–1685.

Keywords: taste receptors, chemosensory receptors, inflammation, ecological sensing, human biodiversity, metabolic diseases, niche construction

Introduction

Across evolution, many mechanisms have evolved to ensure organismic survival to environmental stresses and to optimize reproductive success in changing environments, which for humans includes highly diverse cultural settings. Stresses induced by both cognitive and noncognitive stimuli can influence different organs and systems of the body that communicate with each other to allocate energy to mount an integrated response to them (1). Optimizing the stress response requires the simultaneous activation of 2 interconnected processes: *1*) inflammatory responses and *2*) ecological sensing.

Inflammation plays a major role in the stress response and in mediating energy allocation. Cultural and external environments (described by the concept of "exposome") profoundly changed across human evolution (2), influencing the "nature" of the inflammatory process and its secondary outcomes. This shifted from being adaptive (when inflammation is limited in time over a period of days/weeks) to maladaptive (when inflammation is chronic and long-lasting over a period of years and decades) (3). An outcome of this maladaptation is the development of harmful biological processes that lead to many modern diseases including a high number of age-related pathologies (4).

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Abbreviations used: CRTC1, CREB regulated transcription coactivator1; GPCR, G protein-coupled receptor; LoF, loss of function; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; PRR, pattern recognition receptor; QS, quorum sensing; SNP single nucleotide polymorphism; T2D, type 2 diabetes; TLR, toll-like receptor.

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Present-day physiology shows the senses comprise a complex assemblage of many molecular structures, essential for such responses. Such structures are involved in olfaction and sensing of nutrients, pathogens, temperature, and light, and are located in disparate tissues and integrate different stimuli, mounting biological responses when required and orchestrating interkingdom communication between a host and the symbiotic organisms that dwell in every human body. A major role in these responses is exerted by taste and chemosensory receptors that have been fundamentally important in human evolution for their roles in recognizing external stimuli through cognitive mechanisms, and in perceiving basic taste sensations (sweet, salty, bitter, umami, and sour and possibly also fat) for identifying potential foods and nutrients (5, 6). However, the definition of taste receptors as only signaling taste is now in question because of the distribution of these receptors in many tissues of the body, and their ability to recognize many epitopes, a phenomenon dubbed "degeneracy" (7). Degeneracy is a fundamental and pervasive characteristic of biological systems (8–10) that indicates that 1 receptor can bind to >1 ligand and that 1 ligand can bind to >1 receptor (9). Moreover, population variability in genetic data on taste and chemosensory genes highlights how phenotypic diversity may be the result of evolutionary dynamics (such as demographic events and local selective pressures) that occurred in the course of human prehistory in specific populations.

Ecological sensing is thus much more complex than previously thought, and the recent literature on physiological sensing is reviewed here, with a new viewpoint that frames chemosensation (and especially taste) as a primary form of evolutionarily integrated sensing in relation to inflammatory processes. This phenomenon, described using the lens of biological anthropology, has implications for human health in the present day, and its role is explored in this article, especially in the context of modern human niche construction and the modern proinflammatory environment.

Although the number of receptors and genes involved in taste and chemosensory perception is very high, it is not the purpose of this review to attempt to describe them all. Rather, we have selected the more relevant receptors for ecological sensing and for which the relations with inflammation and modern chronic metabolic diseases have been described by experimental evidence (**Table 1**).

Current Status of Knowledge

Integrating immune, metabolic, and endocrine signals

Understanding the importance of taste and chemosensory receptors as systemic ecological sensors involves understanding the common evolutionary origin of the immune, endocrine, and nervous systems, evidence for which is both morphological and biochemical. This common origin is supported by the presence of a pool of molecules that are mediators and effectors of the stress response and that are shared by these systems in both invertebrates and vertebrates (11). Many receptors that are able to recode internal and external environmental signals (ecological sensors) follow a bow-tie architecture where many stimuli or inputs are sensed by few receptors, often located in different tissues, in order to minimize the cost of immune-neuroendocrine responses to environmental stimuli and to allocate energy to such sensing in a parsimonious way (12). An example of degeneracy is that of the toll-like receptors (TLRs) that act as pattern recognition receptors (PRRs) able to recognize both self-damage-associated molecular patterns (DAMPs), such as cell debris and misplaced molecules, and pathogen-associated molecular patterns (PAMPs), such as nonself-viral and bacterial products (13). Within this scenario, nutrients and metabolic products of the gut microbiota function as a "quasi-self" and are also sensed by a variety of degenerated PRRs (13).

Systemic ecological sensing became more specialized across evolution in response to major stressors that can affect survival and biological fitness, especially nutrient deprivation and pathogen invasion. Responses are not compartmentalized but are co-ordinated across the entire organism and represent an efficient way of allocating metabolic energy. It has been suggested that metabolic and immune function may have evolved from a common ancestral structure (14, 15), an example of this being the fat body of insects that controls both metabolic and immune responses (16).

Across human evolution, the ecology of nutrition is closely linked to immune function. In particular, nutritional resources are likely to play a central role in setting allocations to maintenance effort, and in defining the intensity and the direction of life-history trade-offs (17). Moreover, in the past, food and water have been consistently rich in external stimuli, especially microbial ones. Food and nutrients have quasi-self-properties, not being part of the body but at the same time requiring tolerance mechanisms in the intestine to food antigens and microbiota epitopes to ensure the survival of the individual hosting the microbiome. The idea that these systems coevolved is supported by cellular studies that show that macrophages (immune system) and adipocytes (metabolism) share many functions. They share common activation, after stimulation, by pathogen-associated molecules, such as lipopolysaccharides (LPS) through TLRs that sense pathogens as well as endogenous damage molecules. Across human evolution, the interconnections between metabolic and immune pathways have been optimized to protect the brain from stress stimuli such as starvation and infection (18, 19).

Taste and chemosensory receptors: many tissues, many functions

The capacity of chemosensory receptors to sense multiple stimuli and to monitor different categories of ligands can be traced across a long evolutionary timescale (20), and to exert this function they are localized in many extraoral tissues (21). For example, the bitter-sensitive neurons of the proboscis of *Drosophila melanogaster* respond to the inhibitory pheromone, 7-tricosene. Activation of these neurons by bitter

TABLE 1 Receptors involved in sensory perception considered in this review and their relation with function and inflammation

CHR	Gene	Family[1]	Taste/food	Metabolism	Inflammation	Temperature
1	*TAS1R1*	TAS1R gene family includes 3 members	Umami	TAS1R1 and TAS1R3 sensing of amino acid availability and autophagy (22–24)	Indirect effect, altering gut microbiota composition (25, 26)	—
1	*TAS1R2*	TAS1R gene family includes 3 members	Sugar/sweet	Insulin secretion in vitro (27, 28)	Indirect effect, altering gut microbiota composition (25, 26)	—
1	*TAS1R3*	TAS1R gene family includes 3 members	Sugar/sweet, umami, calcium	Insulin secretion in vitro (27, 28)	Indirect effect, altering gut microbiota composition (25, 26)	—
7	*TAS2R38*	TAS2R gene group includes 39 human TAS2R genes	Bitter, PTC, PROP	Thyroid function (29)	Binding of quorum-sensing molecules and activation of innate immunity (30, 31)	—
8	*TRPA1*	There are ∼28 TRP channels that share some structural similarity to each other	Activated by: Mustard oilWasabiTHC-Garlic (allicin) (32, 33)	Activation of TRPA1 determine insulin secretion in β-cells of the pancreas (34), intestinal motility, serotonin release from enterochromaffin cells (35)	Pain: *Trpa1* is involved in chronic inflammatory diseases such as arthritis (36)	TRPA1 activated temperature <17°C
17	*TRPV1*	There are ∼28 TRP channels that share some structural similarity to each other	Capsaicinallicin (garlic) resiniferatoxin	Role in diabetes and obesity (37)Trpv1 −/− mice, similar to capsaicin-treated animals, exhibit enhanced insulin sensitivity (38). In rodent models of T2D, TRPV1 blockade was shown to halt disease progression and improve glucose metabolism (39)	Pain: high insulin concentrations may activate TRPV1 and lead to hyperalgesia in T2D (40).Role of the vanilloid receptor in inflammatory disorders such as asthma, rheumatoid arthritis, or inflammatory bowel diseases (41–43)	TRPV1 is activated temperature >44°C
2	*TRPM8*	There are ∼28 TRP channels that share some structural similarity to each other	Menthol (44)	Glucose metabolism (45,46)	Pain: TRPM8 activation attenuates inflammatory responses in mouse models of colitis (47)	TRPM8 is activated temperature >25°C
11	*TRPM5*	There are ∼28 TRP channels that share some structural similarity to each other	taste transduction (sweet, bitter, umami)	Regulation of glucose-induced insulin secretion in mice (48). Expression levels of TRPM5 are reduced in obesity and mutations in TRPM5 have been associated with T2D and metabolic syndrome (49)	TRPM5-dependent signals activate tuft cells involved in the initiation of the type 2 immune response (50)	TRPM5 is temperature-sensitive, heat-activated between 15 and 35°C

CHR, chromosome; PROP, 6–n-propylthiouracil; PTC, phenylthiocarbamide; T2D, type 2 diabetes; THC, Δ-9 tetrahydrocannabinol; TRP, transient receptor potential; [1] From HUGO Gene Nomenclature Committee (HGNC).

tasting molecules during the sexual encounter inhibits courting and sexual reproduction, whereas activating them with 7-tricosene in a feeding context inhibits feeding. This taste system monitors different categories of ligands, facilitating or inhibiting behaviors, depending on the context—feeding, sexual reproduction, or hygienic behavior.

Details of taste receptors: TAS1Rs.

Sweet and umami receptors are G protein-coupled receptor (GPCR) proteins from the TAS1R family. Sugar is the most common natural taste stimulus that binds to sweet taste receptors (51). Umami is the "glutamate" taste (typical of the seaweed kombu) initially proposed in Japan in 1908, and more recently taken up in the USA and Europe to describe savory as a taste (in Japanese, umai: savory, tasty; and mi: taste) (52). Heterodimeric receptors of TAS1R1 and TAS1R3 subunits are activated by umami, with TAS1R2 and TAS1R3 activated by sweet stimuli. Lafitte and colleagues (53) have shown that sweet taste receptors are expressed in many extraoral tissues such as those of the pancreas, intestine, and adipose tissue (all with roles in metabolism and insulin secretion) and in the colon, brain, heart, bladder, and immune cells. Furthermore, TAS1R1 has been detected in brush cells, K-cells, L-cells, K/L enteroendocrine cells, and X/A-like cells in the stomach, pancreas, gut, liver, and brain (54). Mice with a knockout for *Tas1r3* have compromised sensibilities for both sweet and umami tastes. Mice lacking *Tas1r3* are unable to increase their expression of sodium/glucose transporters (fundamental for glucose uptake from the intestinal lumen to enterocytes) in response to exposure to dietary carbohydrate. TAS1R1 has also been found to be localized in β-cells in the pancreas: mice exposed to sweeteners show activation of TAS1R2 and TAS1R3 with consequent stimulation of insulin secretion (55, 56). Furthermore, TAS1R3 is also expressed in duct cells of the liver and pancreas suggesting a role in monitoring pancreatic and bile juices (57). In mammals, TAS1R1 and TAS1R3 are also sensors of the fed state and of amino acid availability. If the receptor is knockdown, there is a reduction in the ability of amino acids to signal to mTORC1 (mammalian target of rapamycin complex 1 or mechanistic target of rapamycin complex 1) and the induction of autophagy (22).

Details of taste receptors: TAS2Rs.

Humans perceive bitter compounds by GPCRs from the TAS2R family (58, 59). The expression of bitter taste receptors (TAS2Rs or T2Rs) and their signaling molecules have been identified in several biological systems including the digestive, respiratory, and genitourinary systems (60), as well as in the heart (61), brain, and immune cells, indicating a potential role of these structures for sensing toxic foods and compounds beyond the mouth. TAS2R38 is one of the most studied receptors for bitter taste; in humans, it is present in adipose tissue, thyroid, esophagus, lymphocyte, and epithelial cells. A relation between bitter taste and thyroid function was postulated in 1959 (62), and confirmed more recently in studies where it was shown that TAS2Rs regulate thyroid function, the detection of bitter tasting compounds being linked to changes in thyrocyte function and T3/T4 production (29). TAS2R agonists have been shown to inhibit intracellular concentrations of calcium and iodine, which orchestrate the production of thyroid hormones. A study of 763 women from the Korean population showed thyrocyte-expressed TAS2Rs to be associated with susceptibility to thyroid diseases (63). TAS2Rs are expressed in many tissues, their role being to orchestrate responses in organs that are not directly exposed to external stimuli (such as the thyroid gland). They are expressed in the upper airways, exerting their role in neurogenic inflammation and bacterial clearance. TAS2R agonists increase the beating frequency of cilia in epithelial cells located in the respiratory tract, relax the smooth muscle of lung tissue, and induce the production of proinflammatory and antimicrobial products by macrophages (64, 65). Bitter taste receptors are also expressed in the male reproductive system where they are important for fertility (66–68).

Details of chemosensory receptors: TRP channels.

TRP channels comprise a large superfamily that has 28 members, divided into 7 subfamilies: TRPA (TRP ankyrin), TRPC (TRP canonical), TRPM (TRP melastatin), TRPML (TRP mucolipin), TRPN (TRP NOMPC), TRPP (TRP polycystin), and TRPV (TRP vanilloid). They sense very diverse stimuli including pain, pheromones, and temperature (69), and are expressed in different tissues and cell types including keratinocytes, sensory neurons, melanocytes, and immune cells. In *Drosophila*, they are light sensors, in yeast they perceive and respond to hypertonicity, whereas in nematodes they work as chemical sensors. In humans, TRP channels are activated by molecules present in spices such as garlic (allicin), chili (capsaicin), and wasabi, whereas other types of TRP channel (TRPM8) are activated by menthol, camphor, and peppermint. TRPM5 is a key component of the downstream signaling pathway shared by sweet, bitter, and umami tastes (70). *Trpm5*-knockout mice are not able to perceive sweet, amino acid, and bitter tastes (71) indicating that TRPM5 is required for transduction of these stimuli (72). TRPA1, TRPV1, and TRPM8 are the most studied TRP channels. TRPA1 is an ion channel activated by pungent irritants such as mustard, garlic, and cinnamon. It is also involved in pain perception and pain hypersensitivity as demonstrated in *Trpa1*-deficient mice. TRPA1 is also activated by a wide range of environmental irritants such as vehicle exhaust, that, in combination with endogenous proalgesic agents, elicit inflammatory pain (73), as well as being involved in the perception of cold temperatures (74, 75). Many studies that have linked pain perception and taste are explained by the overlap between the brain regions involved in both, and some studies have demonstrated that pain tolerance seems to increase during exposure to sweet taste (76–78).

TRPM8 is an ion channel that recognizes menthol and several cooling agents, including icilin and eucalyptol, and is activated by low temperature. TRPV1, expressed on a major subset of nociceptive sensory neurons (C and A δ fibers), is activated by capsaicin and hot chili. TRPV1 and TRPA1 are coexpressed in sensory neurons and are involved in the transmission of inflammatory stimuli by nociceptors (damage-sensing sensory neurons). Many ligands can activate TRPV1, including exogenous ligands from the external environment (for example, capsaicin in chili pepper) but also endogenous ligands (including anandamide, *N*-arachidonoyldopamine [NADA], *N*-oleoyldopamine, and leukotriene B4, prostaglandin E2). TRPV1 is also expressed in the nervous system in somatosensory neurons, in the kidney, in the gastrointestinal tract, and in immune cells (79, 80).

Taste receptors modulating communication between two or more ecosystems

Taste receptors are located in "strategic" tissues for ecological surveillance—the gut, immune system, mouth, and nervous system. Their different functions are ancient in evolution. *Drosophila melanogaster* for example, detects bitter molecules through a specific pool of neurons, distinct from those responding to sugars or to other stimuli, with the effect of inhibiting feeding behavior. The activation of bitter-sensitive neurons also induces grooming, the wings and legs of *Drosophila* carrying bitter sensitive neurons that sense Gram-negative bacteria such as *Escherichia coli* (20). Grooming in social insects is a behavioral defense against pathogens and parasite infection, with chemosensory receptors sensing LPS initiating grooming. In humans, taste receptors can also sense bacterial composition (symbiotic bacteria as well as pathological) through *quorum sensing* (*QS*), which is a mechanism of cell-cell communication (also interspecies communication) that modulates changes in gene expression caused by variations of cell density via small diffusible signaling molecules. It is also the biological mechanism that regulates social interactions between bacteria and shapes the behavior of bacterial communities (81). Through QS, bacteria synchronize population behaviors including biofilm formation and exoenzyme production to optimize population growth and survival in different environments (82). Taste receptors can monitor and sense the same mediators produced by bacteria, and thus are fundamental to interkingdom communication, where immunity also plays a crucial role (tolerance in the case of symbiotic bacteria or mounting an immune response in the case of pathogenic bacteria) (83,30).

Interkingdom communication is fundamental for symbiotic bacteria such as gut bacteria to signal the host (gut-host), in terms of appetite and feeding behavior, to sustain bacterial population size, and, for the host, to obtain energy (in terms of ATP) from gut bacteria (see **Supplementary Material 1** for detailed mechanisms on the link between taste receptors and symbiotic bacteria).

A second example of interkingdom communication concerns the relation between a host and opportunistic bacteria. The bacteria-derived toxin LPS is able to induce an inflammatory response in the tongue, in association with decreased taste progenitor cell proliferation, shortened lifespan of taste bud cells, and reduced taste response, especially to sucrose (84–87). LPS also influences sickness behavior which can involve lethargy, depression, anxiety, malaise, loss of appetite, sleepiness, and hyperalgesia. The induction of such behaviors may have an evolutionary basis, with reduction of social interaction limiting pathogen spread (88). For more examples see **Supplementary Material 2**.

The TAS1R2/TAS1R3 receptor recognizes a wide range of sweeteners but exhibits stereoselectivity for certain molecules. For example, it is activated by D-tryptophan but not L-tryptophan (89). D-tryptophan is produced by probiotic strains of bacteria and is involved in immune function (90), decreasing the production of T helper 2 (Th2) cytokines and chemokines in human peripheral and murine immune cells and modulating allergic airway disease in mice (90). TAS2R and TAS1R work in synergy in response to infection, the immune system and metabolic function being modulated simultaneously in response to pathogens (13, 14). A mechanism in which TAS2R and TAS1R work together to sense epithelial infection has been hypothesized (30). TAS1R2/3 may act as a "rheostat" for controlling the magnitude of the TAS2R response according to glucose concentration in the airway surface liquid. Depletion of glucose by bacteria may signal the onset of a possible infection and play a role in the activation of TAS2R and subsequent secretion of antimicrobial peptides (30).

These responses may also be activated by infection with the parasitic helminth *Trichinella spiralis*. This helminth can activate a signaling pathway in intestinal tuft cells similar to that involving TAS2R bitter-taste receptors and TRPM5, initiating type 2 immunity (91). TRPM5, a cation channel that it is essential for the transduction of bitter, sweet, and umami tastes, is expressed in tuft cells, which use taste receptors and other surface proteins to sense pathogens, releasing chemical products to activate an immune response (tuft cells have the capacity to produce an unusual spectrum of biological effector molecules, including IL25, eicosanoids implicated in allergy, and the neurotransmitter, acetylcholine). TRPM5-dependent signals activate tuft cells involved in the initiation of the immune response following parasite infection, producing IL25 which promotes the rapid expansion of type 2 innate lymphoid cells (ILC2) (92, 50). Experiments in mice have shown that the disruption of chemosensory signaling weakens the ability to respond to parasitic infections (50). In recent years, tuft cells have been discovered in the gastrointestinal tract and thymus, and are sentinels for the detection of pathogens and allergens that are inhaled (93–95).

Thus, taste receptors may be part of a set of ecological-sensing mechanisms involved in the systemic response to internal and external stimuli. Communication between organs is mediated by taste receptors that constitute the first sensors in the mouth as well as in other organs.

Genetic variability in ecological sensing: population-specific variability

The varied and various functions described in the previous sections must be contextualized according to the human population, as the genetics of some of these receptors vary between groups. Different evolutionary factors, including drift, migration, and adaptation to local environments, have created population-specific genetic variability in taste perception. Cultural and immunological stimuli in the past may have shaped genetic variability of taste genes and, in turn, food perception and susceptibility to disease. *TAS1R* sequences have been relatively conserved in evolution (96). Genome sequences of bitter taste receptors (*TAS2Rs*) vary among species, omnivorous mammals having the largest *TAS2R* gene repertoire (96). Taste receptors have high levels of segregating loss of function (LoF) variants, these being among the most diverse in the human genome (97). Fujikura investigated LoF variant frequency in 14 ethnically diverse human populations, showing that in taste receptors (including *PKD1L3, PKD2L1* genes) LoF variation (2.10%) is many times higher than overall frequency in the human genome (0.16%), this difference being highest for sour and bitter taste receptors (14.7% and 1.8%, respectively). Thus, individual differences in taste perception may be, in part, due to LoF variant frequency in taste receptors.

Genes involved in taste perception have different evolutionary histories that cannot be generalized, although *TAS1R1* and *TAS1R3* show patterns of diversity that are compatible with positive selection (98, 99). Two single nucleotide polymorphisms (SNPs)—rs307355 and rs35744813—located upstream of the *TAS1R3* gene are associated with sucrose perception, and functional experiments have shown that rs307355-T and rs35744813-T affect gene transcription, silencing promoter activity and modulating sucrose sensitivity. Both SNPs exhibit gradients across Eurasia, with East Asian populations having the highest frequencies and Western European populations the lowest. These 2 noncoding SNPs explain 16% of population variability in human sweet taste perception (100). The sweet taste receptor polymorphism Val191Val in *TAS1R2* is associated with higher carbohydrate intake and hypertriglyceridemia in a west Mexican population (101). Taste receptor gene polymorphisms may therefore be upstream factors influencing chronic metabolic disease expression in populations where alleles associated with food consumption behaviors, which create preferences for foods rich in sweetness, are at high frequency.

Food preferences and sugar intake are linked to many factors in addition to taste and chemosensory receptors, but a detailed description of food intake is beyond the scope of this review, focused as it is on receptors. In **Supplementary Material 3** we discuss 2 genes, *FTO* and *FGF21*, in relation to food intake, taste perception, and metabolic impairment (obesity and T2D), because of their greater importance.

Genetic variability of bitter taste genes such as *TAS2R16* and *TAS2R38* increased in human evolution after the divergence from chimpanzee as well as in more recent times, when *Homo sapiens* faced the challenges of living in new environments. Human taster and nontaster alleles, for example, diverged around 1.5 million years ago (102). The high genetic variability of the *TAS2R38* gene rs713598 in different human populations may be due to ancient balancing selection that took place before Out-Of-Africa, and present-day variation may be due to more recent demographic events (103, 104). Three SNPs located in this gene (rs714598, rs1726866, and rs10246939) at positions encoding amino acids 49, 262, and 296 represent the most common variant alleles of TAS2R38, and determine 2 of the most common haplotypes PAV (Proline, Alanine, Valine) and AVI (Alanine, Valine, Isoleucine) that correlate with bitterness perception. The PAV/PAV haplotype is associated with the supertaster characteristic at the extreme of taste perception as these individuals perceive PROP (6–n-propylthiouracil) to be more bitter than others. It also confers more efficient bacterial clearance, increasing nitrous oxide production and clearance through the movement of cilia in the upper respiratory tract. The same 3 SNPs that define the PAV-AVI haplotype are associated with dental caries, one of the possible causes of blood infection or death in the past, and a source of inflammatory molecules that accelerate the process of atherosclerosis and coronary artery diseases (CAD) in the present day (105, 106). The PAV/PAV haplotype protects against caries, but this protection declines with human aging (107). *TAS2R38* modulates innate oral immunity in a *TAS2R38* genotype-specific manner, being differently regulated by various types of bacteria in the oral cavity (108); this is an example of coevolution between humans and oral microbes (109). Moreover, *TAS2R38* plays a critical role in the response to QS molecules produced by Gram-negative bacteria such as the respiratory pathogen *Pseudomonas aeruginosa*. Cultures derived from tasters (PAV/PAV) exhibit the strongest response to pathogens, whereas cultures from nontasters (AVI/AVI) and heterozygous individuals (PAV/AVI) have nearly undetectable responses (31) (see Supplementary Material 2 for details).

A study performed in a cohort of centenarians recruited in Sardinia (in the Longevity Blue Zone) showed an association between genetic variants located in the *TAS2R38* gene and human longevity. It was suggested by the authors of this study that PAV/PAV individuals may have a favorable genetic condition for the attainment of exceptional longevity (110).

Variants in *TAS2R16* are associated with salicin perception, arising 1.1 million years ago in East Africa, conferring evolutionary advantage to those exposed to a wider range of bitter compounds (111). The rs860170 is a SNP located in *TAS2R16* differentiates populations and the rs860170-A allele is highly predominant in North African populations and is also associated with salicin bitterness perception (112). This is in line with the findings of Soranzo and colleagues (113), who detected signatures of positive selection at *TAS2R16* according to the geographic patterns of its variants. Campa and colleagues (114) described a haplotype including *TAS2R16* rs860170-A which is associated with longevity in humans, arguing that salicin could have similar effects to aspirin, acting as an anti-inflammatory agent and therefore favoring healthy aging. Few studies exist on the genetics of taste in centenarians (115). It is difficult to retrieve phenotypes linked to taste in very old people, and to our knowledge there is only one study that describes taste perception in very old age performed on 126 centenarians and 100 elderly subjects (mean age 70.5 ± 5.0 y). This study showed a general and significant decline in taste sensitivity, sweet taste perception being the most preserved in centenarians (116).

The *TRPM8* rs10166942-T allele shows strongly differentiated frequencies in human populations, from 5% in Nigeria to 88% in Finland (117). This differentiation may reflect variation in climate as well as variation in factors that correlate with climate, such as diet, subsistence strategy, and pathogens. There is strong evidence for local adaptations in *TRPM8* that correlate with latitude and temperature (117). The T allele of this gene was present in prehistoric European groups (hunter-gatherers, farmers, steppe pastoralists), there being evidence for recent local positive selection in all non-African populations (117). The SNP is strongly associated with migraine in Europeans, with the ancestral C allele being protective of migraine with and without aura. Mechanistic insights based on *TRPM8* expression data showed a genotype-dependent influence on cold pain sensation suggesting that carriers of the reduced migraine risk allele have reduced sensitivity to cold stimuli and that *TRPM8* acts as a cold thermosensor and cold pain transducer in humans (118).

Ecological sensing, taste/chemosensory receptors, chronic inflammation, and "modern" diseases

Chronic inflammation and modern human niche construction.

Modern human niche construction in postindustrialized societies are characterized by "new" diseases (transition from communicable to noncommunicable diseases) such as obesity, cardiovascular diseases, T2D, and age-related impairment whose common and shared characteristic is chronic inflammation (13, 14, 119–121).

In this section, we describe how taste/chemosensory receptors and inflammation are interconnected and how inflammation may impact and impair proper ecological sensing that, in turn, sustains the inflammatory process through human behavior, determining multilevel responses and a vicious cycle detrimental for health. Before mentioning some experimental examples of the relations between inflammation and taste/chemosensory receptors there are two ecological considerations that influence the extent to which new niche construction may increase susceptibility to diseases through chronic inflammation. These are described by evolutionary mismatch theories (122, 123):

1) inflammation highly impacts energy allocation (modulating energetic homeostasis at different organs and systems and many molecular mechanisms have evolved to counteract acute inflammation and sepsis—rapid response), whereas chronic inflammation, both in terms of magnitude and duration, is detrimental to health (119, 121);

2) modern humans evolved in environments profoundly different from the present day, never experiencing nutrient excess. Improved access to food resources and the emergence and rise in use of antibiotics and vaccination have profoundly increased life expectancy but have also profoundly changed human ecological interactions.

Obesity constitutes the best example of the link between new niche construction, chronic metabolic inflammation, called metaflammation (14, 15, 124, 125), and taste receptor impairment.

Taste dysfunction among obese individuals is a product of such systemic inflammation; in mice, reduction of inflammatory tone is crucial to the maintenance of the function of these receptors (126). This has implications for taste preference among people carrying excess body fatness. The perception of certain foods rich in sugars activates mechanisms of strong reward, motivating consumption of such foods (and thus likely contributing to sustained metaflammation). Taste receptors trigger specific behavioral responses, the expression of human TAS1R2-receptor in mice generates animals with humanized sweet taste preferences (127).

Taste sensing influences human behavior and decision-making, while at the same time influencing immune and metabolic processing and signaling across organs, through inflammatory responses.

Taste, chemosensory receptors, and chronic inflammation: a vicious cycle.

TAS1R1, TAS1R2, and TAS1R3 are not directly activated by inflammatory molecules, but are crucially involved in chronic inflammatory diseases, including T2D. This is because they are expressed in the brain (influencing food choice), in the gastrointestinal tract, in the kidney, and in adipose tissue, where they influence metabolic processes such as insulin secretion, and glucose and fat metabolism (128, 129, 27). Overnutrition affects taste perception, obese individuals needing greater stimulus to activate taste receptors for the same hedonic response that nonobese subjects have (28). Nonnutritive sweeteners (NNSs) such as saccharin, aspartame, acesulfame-K, and sucralose, provide a sweet taste with few or no calories, but trigger the same hedonic response as sugars and activate sweet taste receptors in the same way. This may have several metabolic outcomes, impacting on glucose and lipid metabolism as well as bone health, adipogenesis, and reproductive function (130). For example, consumption of acesulfame-K for 4 wk can alter gut microbiota composition towards a proinflammatory state (131), whereas sucralose consumption can induce changes in proinflammatory genes, promoting inflammation (132). A recent study placed attention on the role of the kidney in sweet taste sensing and subsequent regulation of inflammasome signaling. The inflammasome is a multiprotein complex located in the cytoplasm of the cell that is responsible for the maturation of proinflammatory cytokines, and high glucose concentrations induce the generation of reactive oxygen species (ROS), which is one of the first identified triggers of NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome activation, in part via sweet taste receptors (133).

TRPA1, TRPV1, and TRPM8 play crucial roles in the inflammatory process, there being complex interactions between inflammation, the immune and nociceptive systems. TRPA1, a somatosensory receptor for exogenous irritants ingested from food, is also activated by endogenous inflammatory signals (134). TRPA1 channels are required for the release of inflammatory neuropeptides (causing pain), being activated by many inflammatory agents from nonneuronal cells of the skin, airways, and gastrointestinal tract, among other tissues (135). TRPV1 and TRPA1 are also involved in the most common inflammatory disease which affects the airways, asthma. Inhibition of the 2 genes for *TRPV1* and *TRPA1* results in complete reduction of airway hyperresponsiveness in both allergic and nonallergic mouse models, suggesting a link between exposure to irritants and increased airway sensitivity (136–138). TRPA1 is also involved in the chronic inflammation of colitis (139).

TRPV1 plays an important role in glycemic control (37), loss of control of the activity of TRPV1 being implicated in pathogenetic mechanisms of both type 1 (140) and type 2 (141) diabetes. TRPV1 agonists increase carbohydrate oxidation, increase the consumption of oxygen in muscle cell, and stimulate both mitochondrial activity and fatty acid oxidation (142). Activation of TRPV1 channels by dietary capsaicin triggers browning of white adipose tissue, offering a possible molecular strategy for counteracting obesity (143). The activation of TRPV1 in brown adipose tissue enhances the expression of SIRT-1 (sirtuin 1), which facilitates the deacetylation and interaction of PPARγ (peroxisome proliferator activated receptor gamma) and PRDM16 (PR/SET domain 16), enhancing metabolism and energy expenditure (144).

Human adipocytes express TRPV1, and its activation causes the release of inflammatory cytokines in white adipocytes (145), but not brown adipose tissue. TRPV1 is involved in the pathogenesis of atherosclerosis (a common chronic inflammatory condition), treatment with a TRPV1 agonist promoting cholesterol efflux in the foamy macrophages of atherosclerotic aortas of apoE-deficient mice (80). TRPM8 is involved in preventing abnormalities in glucose metabolism, probably because of increased energy expenditure with its activation (146). TRPM8 has anti-inflammatory capacity (47); its expression, induced by either cold stress or menthol, exerts an inhibitory effect on TNFα, mediated by NF-kB (147), inhibiting the inflammatory response. The combined roles of TRPA1, TRPV1, and TRPM8 in inflammation have been examined in evolutionary perspective by Straub (148), taking a lead from evolutionary medicine (149,150). *TRPV1*, *TRPA1,* and *TRPM8* genes may have been positively selected during human evolution for their role in acute inflammatory processes. TRP channels have the role of orchestrating a systemic response of all the organs in order to ensure survival from exposure to acute stressors. These channels transmit and collect information from peripheral inflammation to the central nervous system, which then orchestrates appropriate energy allocation from adipose tissue stores, skeletal muscle, and the liver to the activated immune system. In chronic inflammation, the immune system is constantly stimulated (sometimes also through sterile stimuli that come from the body itself) (151), and continuous nonspecific TRP responses propagate inflammatory stimuli that are the basis of many age-related diseases (for more details see "garb-aging theory") (151). Given the role of taste genes in chronic inflammation, and that one of the central mechanisms in aging is inflammaging (119), it is not surprising to find studies that highlight the role of these sensors in longevity (152). *Trpv1* mutations protect against diet-induced obesity in animals fed with high-fat diets (153), also increasing longevity (154). Riera and colleagues (154) have identified novel neuroendocrine circuitry that affects aging and longevity, and whose main actors are *TRPV1* genes. *Trpv1* mutant mice have been shown to have a youthful metabolism at old age; a genetic deletion of *Trpv1* not only regulates the activity of CREB regulated transcription coactivator 1 (CRTC1) in peripheral sensory neurons, but also improves glucose tolerance and increases energy expenditure throughout aging. In sensory neurons, TRPV1 integrates multiple sensory inputs and transduces them into neuroendocrine signals that regulate the activity of CREB/CRTC1 that, in turn, modulate metabolic activity. This is compatible with recent data on centenarians, who have metabolically healthy phenotypes that are similar to those found in adults following a calorie-restricted diet (13, 155). More examples of the complex relations between ecological sensing, taste, and inflammation are reported in **Supplementary Material 4**.

These taste and chemosensory receptors are thus broad ecological sensors important in many systems and organs linked with inflammation (see Table 1 for a general overview). We report a method of visualizing these links in **Figures 1** and **2**. Figure 1A and 2A show networks based on protein-protein interactions [based on STRING (156)] for TAS1Rs/TAS2Rs and TRPs, respectively. Figure 1B and 2B show the genes that encode for the proteins reported in the networks and their involvement in different pathologies [according to DISEASES (157)]. For network 1 (Figure 1A) 5 genes are associated with the common cold, obesity, and diabetes mellitus, whereas for network 2 (Figure 2), 6 genes are closely associated with migraine and pain agnosia. Inflammation plays a major role in the vast majority of the pathologies listed in both networks (see **Supplementary Table 1** and **Supplementary Table 2** for the entire list of pathologies and related genes). A detailed description of the method is reported in **Supplementary Material 5**.

Social implications of taste variation

Population genetic variation in taste perception has been shaped by human social evolution. In turn, the major patterns of human social evolution have been shaped by changes

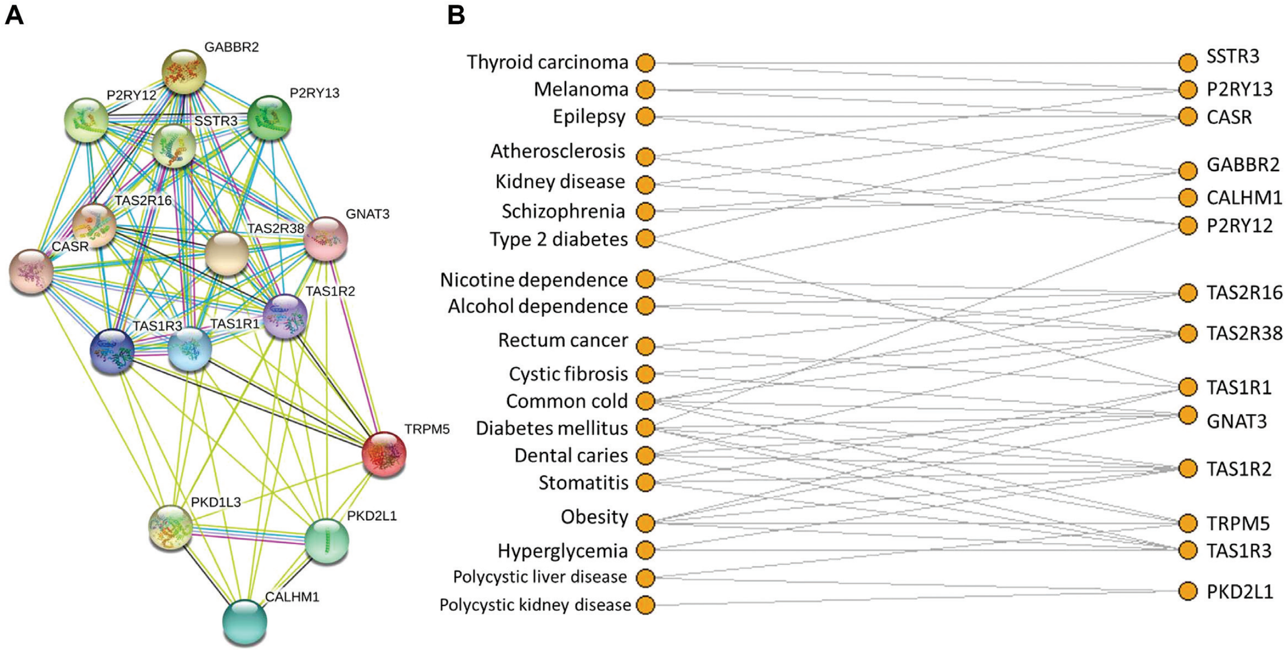

FIGURE 1 (A) Interactions between TAS1R1, TAS1R2, TAS1R3, TAS2R38, TAS2R16, and other receptors with disease or disorder. Edges represent protein-protein associations. (B) Names of the genes involved in pathology are according to the DISEASES database. Only pathologies that have ≥ 3 connections with proteins of the network are reported.

in the environment or changes in the ecological relations between humans and their resources (158). Taste receptors operate within integrated interactive biological systems—immunological, endocrine, and nervous—which are fundamental to human ecological success. Aspects of human social evolution, including increased range size, meat eating, cooking, sociality, and technology-use would have influenced taste receptor function through socially mediated exposure to pathogens and food through consequent changes in gut microbiota. These influences would have been mediated at

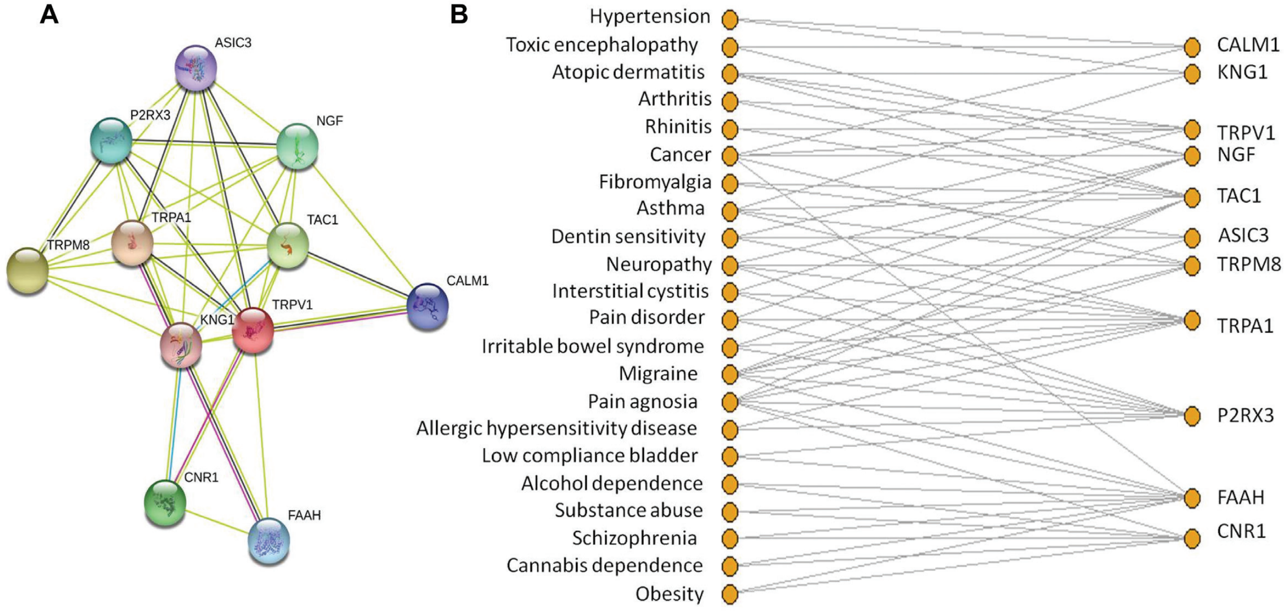

FIGURE 2 (A) Interactions between TRPV1, TRPA1, TRPM8, and other channels with disease or disorder. Edges represent protein-protein associations. (B) Names of the genes involved in pathology are according to the DISEASES database. Only the pathologies that present ≥ 2 connections with proteins of the network are reported.

a higher level through human niche construction, which would have accelerated the control of the environment by adding ecological inheritance (159) to genetic inheritance. Ecological inheritance includes social transmission and inheritance of cultural knowledge and material culture and can include horizontal gene transfer of microbiota between members of the same communities.

Ecological inheritance would have helped to create distinct niches which would have accelerated the coevolution of ecological sensors to environmental stimuli. Such coevolved systems might have operated in reasonable balance until the origins of agriculture, which would have been a major disruptor of existing local coevolved structures. As well as being the key evolutionary transformation in the history of humanity (160), the origin of agriculture had broad-reaching effects on human diet (161). Starting from around 10,000 y ago (according to location) radical economic, societal, and technological change saw agriculture become the dominant mode of provisioning for the majority of the world's populations (162). With this came the dominance of grains and other carbohydrate-rich foods in most human diets. The ability to produce surpluses of grain set the conditions for the development of religion, government, and social and economic inequality (162), all cultural forces that have shaped human niche construction since. The emergence of agriculture as an economic system led to the spatial concentration of homogeneous resources and an intensification of food production, storage, and technological development (163), which further intensified niche construction in response to changing relations between energy content and micronutrient content of the diet, and established closer relations between humans and potentially pathogenic bacteria increased (164).

Human disease in history and prehistory is closely tied to the changing size and density of human populations and the behaviors that promote disease transmission (165). Natural selection for resistance to infectious disease was underway well before the advent of agricultural society (166) and it is unlikely that this took place against specific pathogens as we know them now. Rather, genetic adaptations are likely to have emerged in response to sets of pathogenic agents within local ecologies, and the adaptations to disease we see today are relics of the past. Using HapMap project data, Amato et al. (167) identified positive selection to have taken place against disorders that can be grouped as being of hematological, infectious, and immunological nature, respectively.

Although it is common to think of taste receptors, the immune system, and the microbiome residing within individuals, humans are intensely social and have evolved to best live in groups (168). Although individuals can make choices with respect to their energy intake and the biodiversity represented in the food they choose, humans prefer to eat commensally (169). Such commensality not only influences what individuals may choose to eat, but also the microbiota they inevitably share with other people. The microbiota of an individual is not an isolated community, but is rather more similar within human communities than between them and in certain nonindustrialized regions, such as in Papua New Guinea and Tanzania (170), bacterial dispersal also shapes the microbiomes of unrelated individuals (171). A study in mice has shown that conditions of cohousing of coprophagic mice influences their gut microbiota composition (172). In humans, the microbiota of cohabitating individuals increases similarly, indicating that the transfer of gut taxa occurs most between individuals of the same family, including also their dogs (173). As biocultural beings, humans embody their social environments, and the inequalities therein (174). People of low socioeconomic status are more likely to consume more cheap, energy-dense, nutrient-poor processed foods (175), as they struggle with food insecurity and food poverty, and are forced to satiate chronic hunger with inexpensive, nutrient-poor foods (176,177). As the microbiome depends on the types of food consumed, people embody inequality at the level of the gastrointestinal tract. Taste is thus shaped according to food availability and affordability, niche construction influencing taste diversity in yet another way.

Conclusions

Physiological taste is much more than taste. Taste receptors and chemosensory receptors are complex ecological sensors that can be modulated by many stimuli from different systems, and which orchestrate interkingdom communication. Many receptors and genes involved in taste perception are shaped for complex ecological sensing, and their stimulation not only has an impact on gustatory perception and dietary behavior, but also on the inflammatory process and health, their activation having important influences on the immune, metabolic, and nervous systems. **Figure 3** is a summary illustration of the relations between bodily internal and external environments, and the ways in which taste receptors and channels mediate both behavior and inflammation in maintaining a coadapted state, which is evolutionarily stable and extremely responsive to environmental change. These receptors show considerable genetic variability between human populations, reflecting the history of populations and the genetic backgrounds of individuals within them, as outcomes of demographic change and past adaptations. Humans always profoundly change their surrounding environments, which in turn affect their biology. Ecological sensing is pivotal to survivorship, but major human ecological disruptors in the present day (which include consumption of ultraprocessed foods and diets high in energy density and sweetness) impact on these receptors, influencing communication among organs and causing elevated inflammatory tone. Such elevated inflammatory tone is central to many modern, chronic metabolic pathologies such as T2D, obesity (metaflammation) and also to age-related diseases (inflammaging). We argue that these receptors—because of the degeneracy that makes them excellent ecological sensors—may be potential targets for modulating inflammatory levels in different diseases where inflammation plays a major role (178).

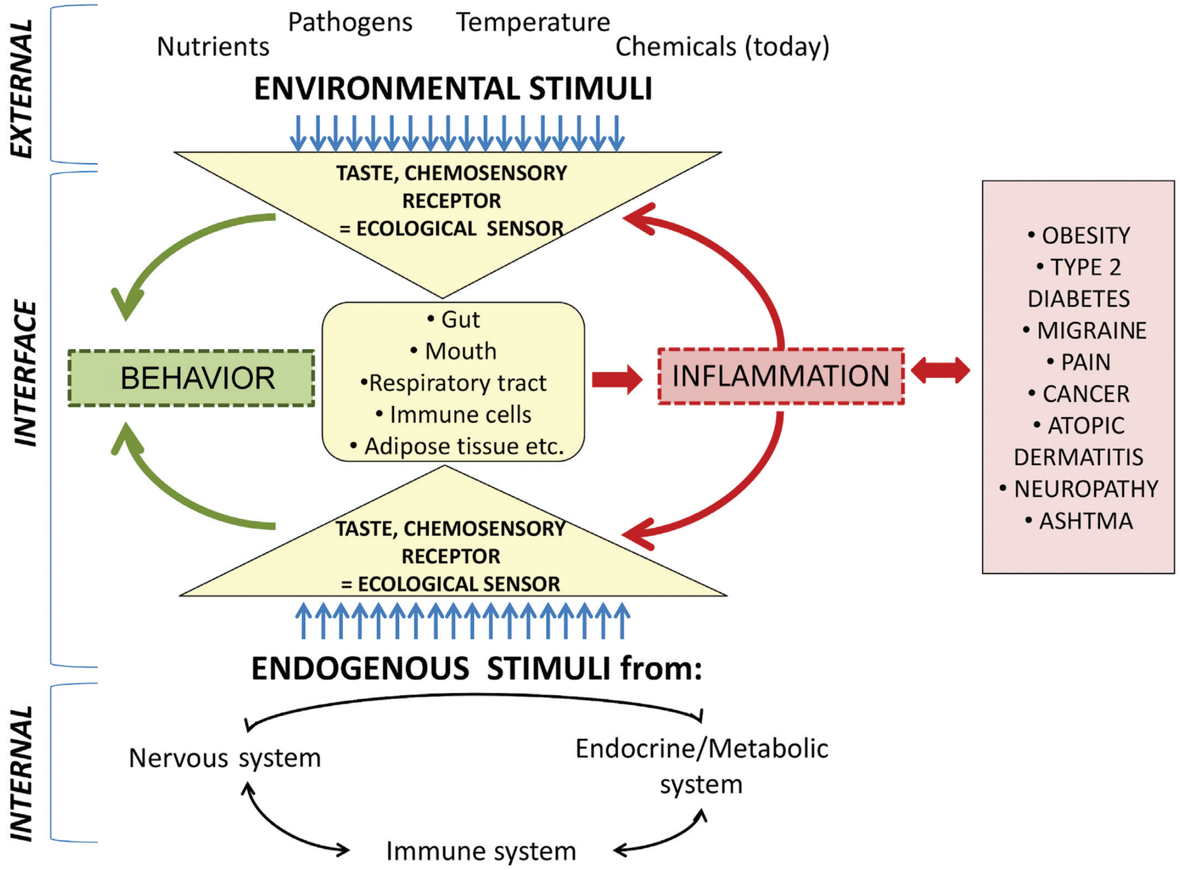

FIGURE 3 Overview of dynamics of ecological sensing through taste and chemosensation that mediates inflammation. A high number of external and internal stimuli converge on taste and chemosensory receptors, which are in effect ecological sensors for a variety of stimuli or molecules able to bind to them. The figure reports a bow-tie architecture with many stimuli that converge on the same pool of receptors able to sense many ligands – a phenomenon known as "degeneracy." These receptors are found in many tissues and organs, orchestrating and integrating communications among them with impacts on human behavior. The rapid and recently changing environments of the present day create new selective pressures that impinge upon these sensors (that have been shaped during evolution by other stimuli) and can increase inflammatory tone, a molecular biomarker of many modern diseases such as obesity and T2D. In red are reported a list of pathologies according to a network-based approach that highlight the role of these receptors in apparently distinct pathophenotypes (the reported pathologies are not all those possible but we selected those linked to the receptors described in the present review).

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