VOLUME 97, NO. 2 JUNE 2022

THE QUARTERLY REVIEW
of BIOLOGY

TASTE AND SMELL: A UNIFYING CHEMOSENSORY THEORY

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The Quarterly Review of Biology, volume 97, number 2, June 2022.
https://doi.org/10.1086/720097

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KEYWORDS
chemical senses, receptors, ligands, chemosensory systems, evolution of chemosensation, chemical ecology

ABSTRACT

Since antiquity, the sense of smell (olfaction) is considered as a distance sense, just like sight and hearing. Conversely, the sense of taste (gustation) is thought to operate by direct contact, similarly to touch. With the progress of natural sciences, information at molecular, anatomical, and neurobiological levels has also contributed to the taste-smell dichotomy, but much evidence inconsistent with a sharp differentiation of these two senses has emerged, especially when considering species other than humans. In spite of this, conflicting information has been interpreted so that it could conform to the traditional differentiation. As a result, a confirmation bias is currently affecting scientific research on chemosensory systems and is also hindering the development of a satisfactory narrative of the evolution of chemical communication across taxa. From this perspective, the chemosensory dichotomy loses its validity and usefulness. We thus propose the unification of all chemosensory modalities into a single sense, moving toward a synthetic, complex, and interconnected perspective on the gradual processes by which a vast variety of chemicals have become signals that are crucially important to communication among and within cells, organs, and organisms in a wide variety of environmental conditions.

Introduction

CHEMICAL sensing allows all cells, organs, and organisms to get and share information that is crucial to many different biological activities. When it represents the outer world (exteroception), chemical communication is split into two main senses, taste and smell. Both of these senses rely, however, on interactions of chemosensory cues with molecular receptors, so that one can legitimately wonder whether a real need for a binary representation of chemosensation exists. Actually, all visual perceptions pertain to one sense, sight, which uses light reflected or emitted by objects to explore the surrounding environment. Hearing is also considered a single sense, but is specifically devoted to perceive sounds, while touch is dedicated to the detection of mechanical stimuli. Why is chemosensation so special that it requires a further subdivision in other senses? Certainly, the vast structural variety of chemosensory substances requires a large number of different molecular receptors and cannot be classified by using a simple parameter such as wavelength or frequency (Su et al. 2009). But it is not reasonable, a fortiori, to reduce all possible molecular interactions involved into just two sensory categories. Accordingly, one can argue that the main reason for a further categorization of chemosensation lies in the fact that two different organs are employed for chemosensory perceptions in humans, the tongue and the nose, providing information about either material already in the mouth or distant objects, respectively. Actually, the taste buds on the tongue and the olfactory epithelium at the roof of the nasal cavity contain chemosensory cells that are assumed to respond to different chemical stimuli, generating impulses that travel along so-called gustatory or olfactory nerves to the brain, within specific signal transduction mechanisms and processing pathways. Overall, such a differentiation is currently adopted as the default premise for all studies on human chemosensation, including the approaches to critical biomedical issues. However, a third chemosensory modality is considered as well, known as "chemesthesis," involved in the detection of stimuli that activate nociceptive fibers. For example, examining COVID-19-associated multimodal chemosensory impairments, it has been stated that "[t]aste and chemesthesis are senses that are distinct from smell, even though all three combine to tell humans what 'flavour' a food or beverage has" (Marshall 2021:342). Indeed, multimodal experiences of flavor can arise by the integration of gustatory and olfactory stimuli with pain, touch, and thermal sensations that do not fit into the traditional taste-smell differentiation. In spite of this, by pinching the nose while tasting, any person can qualitatively interpret lingual, nasal, or retronasal events as olfactory or gustatory sensations, albeit with substantial interindividual variations that prevent a clear distinction. However, such a dichotomic representation of the chemosensory world has been extended to any sentient form of life, from single-cell to multicellular, and from aquatic to terrestrial organisms. We will discuss here the puzzling ecological and evolutionary implications of this tendency to generalize human traits, wondering if a binary view of chemosensation is really valid and useful in science. For a systematic approach to the matter, the diagnostic criteria on which the taste-smell differentiation is constructed have been summarized as follows:

- *The spatial perspective*: olfaction is a distance sense, assisting in navigation and orientation in an external fluid medium by assessing distributions of chemical cues in time and space, while gustation is a contact sense, detecting chemicals that have already entered the mouth.
- *The molecular perspective*: the two senses are different because they allow detection of different molecules that interact with specific chemosensory proteins.
- *The neurobiological/anatomical perspective*: smell perceptions are mediated by specific organs and neural systems that are morphologically and functionally different from those involved in taste perceptions.

Our discussion will provide evidence that these diagnostic features are not consistent with each other, and are troublesome even when individually considered. It follows that taste-smell differentiation is essentially based on invalid criteria, generating an unnatural categorization of chemosensory processes that prevents the development of a satisfactory narrative on the evolution of chemical communication. Paradoxically, it will also emerge that the taste-smell differentiation does not completely apply even to the human species when considering the ectopic expression of chemosensory genes in inner organs and the chemotactic abilities of both spermatozoa and cells of the immune system. Finally, beyond evolutionary and conceptual implications, we will also ask if differentiation between the chemical senses is really helpful for organizing scientific efforts. By examining the current literature, we conclude, instead, that the taste-smell dichotomy is actually disturbing research on chemosensation, since it introduces a bias in the design and interpretation of experiments, leading to miss or obscure potentially useful information and, in particular, any contrary evidence.

Spatial Differentiation

PREJUDICED ASSUMPTIONS ABOUT THE SPATIAL RANGE OF THE CHEMICAL SENSES

In neuroscience, olfaction is considered a distance sense, since it allows the detection of small volatile compounds released by a source not physically connected with the target organism. Accordingly, smells are thought to play critical roles in animals' olfactory navigation and tracking, allowing it to locate food, identify mates, and avoid predators (Su et al. 2009; Touhara and Vosshall 2009; Pannunzi and Nowotny 2019; Young et al. 2020; Marin et al. 2021). Conversely, gustation is thought to involve direct tactile contact with the emitter of chemosensory cues, providing information about food material already ingested in the mouth, thus acting as a driver of feeding behavior (Hemilä and Reuter 2008; Smith 2008; Yarmolinsky et al. 2009; Boesveldt and de Graaf 2017; Cheok and Karunanayaka 2018). This spatial differentiation can be easily verified by only considering humans and other land animals that sense odiferous compounds transported by air. Among terrestrial vertebrates, "macrosmatic" animals such as dogs, rats, pigs, bears, and elephants recognize sources of smell at a considerable distance, while the same animals detect taste molecules (e.g., sugars) by a direct tactile contact of their tongues with the emitter. Although substantially limited to terrestrial animals, this view led to generalization, accepting as a truism that olfaction is always a distance sense. Such a selection of observations, however, cannot lead to such a universal conclusion. Indeed, contradictions and ambiguities emerge in spatial differentiation when aquatic environments—where water, not air, transports the chemical stimuli—are also considered. The chemosensory cues can actually be differentially transported at a distance in air and water (Mollo et al. 2014, 2017). In extreme cases, volatile compounds are insoluble in water (Figure 1A), where they are instead detected by a "tactile" form of olfaction by fish and crustaceans (Giordano et al. 2017). Consequently, odiferous substances are always detected from afar only on land.

In parallel, the argument that taste is a contact sense is also based on a biased generalization. Terrestrial vertebrates only detect α-amino acids and simple sugars, which are typical nonvolatile taste metabolites, by contact with their taste buds, but marine animals (e.g., sharks) can recognize such compounds at a distance because they are very soluble in water (Tricas et al. 2009). Although the detection of chemosensory molecules always implies physical contact/interaction with the molecular and anatomical receptors that capture them, the above soluble taste molecules can actually travel for long distances in water before reaching the chemosensory systems of a shark. This fact contradicts, however, the assumption that all gustatory substances are detected by contact with the emitter.

BIASES IN CONDITIONAL REASONING: THE "WATERBORNE OLFACTION"

Do the above arguments necessarily imply the complete demise of the traditional and deep-rooted taste-smell dichotomy or can its universality be downgraded to conditional statements that preserve the spatial range of the senses? An attempt in this direction starts from the assumption that volatile compounds

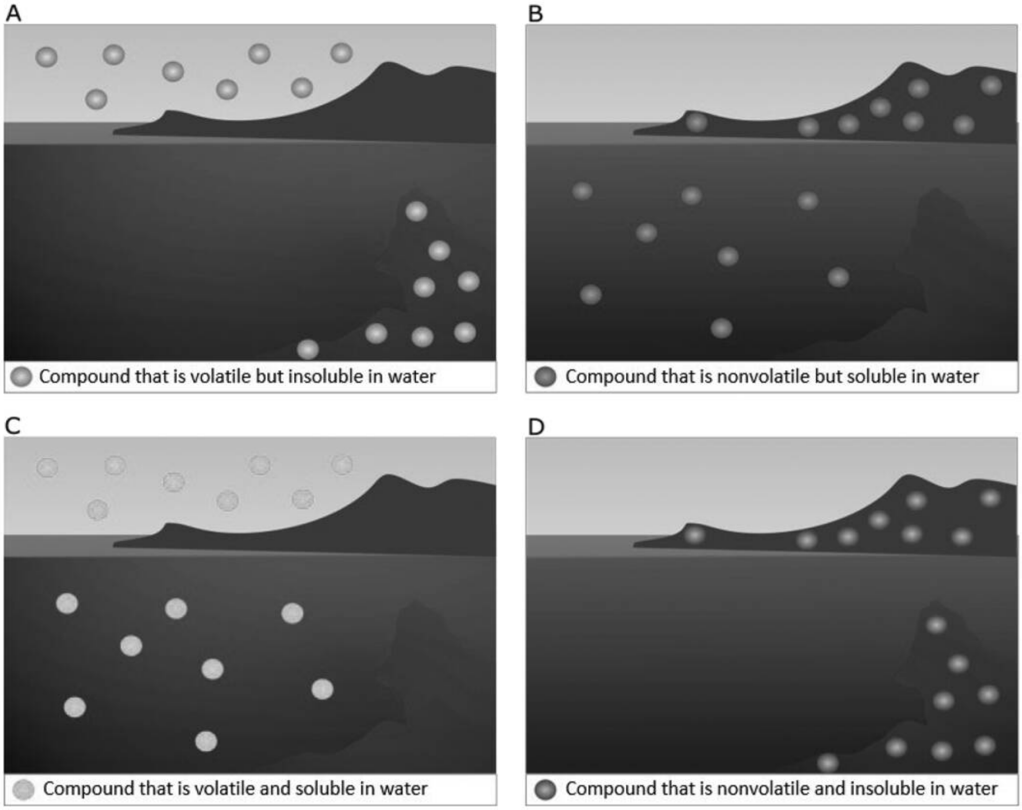

Figure 1. Schematic View of the Spatial Distributions of Chemosensory Molecules According to Their Potential Volatility in Air and Solubility in Water

Chemosensory cues can be classified into types based on their potential volatility in air and solubility in water. Natural situations are somewhere between these ideal extreme cases in A–D. Representative examples of chemosensory molecules occurring both in terrestrial and aquatic environments are reported below, along with their estimated volatility and solubility taken from a recent review (Mollo et al. 2017).

A. Isofuranodiene is a furanosesquiterpene with molecular weight (MW) of 216, estimated water solubility at 25°C of 1.01×10^{-1} mg L^{-1}, and vapor pressure of 7.65×10^{-2} Pa. It is found in marine mollusks and cnidarians and in several terrestrial flowering plants used as fragrance ingredients. Similarly to the ideal compound described in A, isofuranodiene is responsible for olfactory perceptions in terrestrial environments, while it is detected by touch by aquatic organisms (Giordano et al. 2017).

B. α-amino acids have MW ranging from 75 (Gly) to 204 (Trp), estimated water solubility at 25°C between 2.85×10^{3} mg L^{-1} (Trp) and 1.00×10^{6} mg L^{-1} (Asp), and vapor pressure between 2.47×10^{-7} Pa (Tyr) and 1.46×10^{-4} Pa (Glu). As in the situation shown in B, they are not transported by the aerial medium but produce a panel of taste sensations when they come into contact with the human tongue. Instead, they are easily transported by water in aquatic environments stimulating the appetitive behavior of fish and crustaceans (Mollo et al. 2017 and references therein).

C. Cadaverine is an aliphatic diamine with MW 102, estimated water solubility at 25°C of 1.00×10^{6} mg L^{-1}, and vapor pressure of 1.35×10^{2} Pa. Along with putrescine, it is well known for its repulsive odor to humans, while it also acts as a feeding attractant both for rats and fish (Mollo et al. 2017 and references therein). The compound is easily transported by both fluid media (air and water), thus fitting within the situation described in C.

D. Friedelin is a pentacyclic triterpenoid with MW 426, estimated water solubility at 25°C of 6.82×10^{-5} mg L^{-1}, and vapor pressure of 5.19×10^{-7} Pa. It has been isolated from both oak cork and leaves, and from a marine alga (Mollo et al. 2017 and references therein). Friedelin is also the most prominent triterpenoid in cannabis (Russo and Marcu 2017). Triterpenoids are often associated with taste perceptions and, given their high molecular weight and their extremely low solubility in water, need to be detected by touch in both terrestrial and aquatic environments within the situation described in D.

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that are insoluble in water (Figure 1A) can be both “terrestrial smells” and “aquatic tastes,” while nonvolatile but water-soluble compounds (Figure 1B) can act as both “terrestrial tastes” and “aquatic smells.” With reference to olfaction, this has led to the proposition that aquatic and terrestrial vertebrates actually detect opposite bouquets of odorants (Tierney 2015), and to introduce the concept of waterborne olfaction (Hemilä and Reuter 2008). Even accepting this discontinuity for selected groups of chemosensory substances, a spatial differentiation of the chemical senses featuring any possible combination of the distributions of chemical cues in nature becomes impracticable. Actually, only in the cases illustrated in Figures 1A and 1B, chemical cues with opposite physicochemical properties can be detected within “opposite” spatial ranges by terrestrial and aquatic organisms. Instead, in the case of compounds that are both volatile and soluble (Figure 1C), as well as in the case of compounds that are neither volatile nor soluble (Figure 1D), chemosensory molecules are actually detected within “similar” spatial ranges. It follows that a spatial differentiation of the chemical senses cannot simultaneously embrace all four conditions A–D and is therefore unrealistic. The picture becomes even more confused when considering: chemical cues that are neither airborne nor waterborne and disperse in two dimensions on the sea surface; amphiphilic molecules that can move long distances in water when dispersed as colloidal suspensions (micellae); and nonvolatile compounds that are transported in the atmosphere as aerosol particles (Tsoukatou et al. 2001; Zimmer and Zimmer 2008; Mollo et al. 2014).

Knowledge of the actual spatial distribution of chemosensory signals in different environments can greatly contribute to a better understanding of the heterogeneous distribution of species in a variety of habitats (Figure 2). Actually, as illustrated in Figure 1, terrestrial and aquatic species are differentially exposed to chemosensory molecules according to their physicochemical properties. Nevertheless, confusion exists in the marine literature generated by the assumption that all chemicals encountered by fish and crustaceans are transported by water (Hara 1994; Caprio and Derby 2008; Scott 2008). This position does not take into adequate consideration that a huge number of hydrophobic compounds are actually detected in aquatic environments by contact forms of chemical communication (Mollo et al. 2014, 2017; Giordano et al. 2017). However, as we stated above, many of these insoluble compounds are volatile, thus detected at a distance on land. On the other hand, the chemosensory adaptations in amphibians and secondarily aquatic vertebrates, such as whales (Figure 2G) and sea snakes, offers fascinating opportunities to evolutionary biologists when taking into proper consideration not only the spatial behavior of these animals, but also the chemical cues most frequently encountered by them, and their physicochemical properties (Kishida and Hikida 2010). In this perspective, however, a distinction between olfaction and a so-called “waterborne” or “underwater” olfaction requiring molecular interactions with waterborne cues that are traditionally considered to be pertinent to the gustatory modality introduces a puzzling evolutionary discontinuity. Actually, there are proper cases of aquatic olfaction in air-breathing animals that are able to sense hydrophobic odors that adhere to the surface of submerged objects in aquatic environments and are also volatile on land (Figure 1A). The star-nosed mole (*Condylura cristata*) and the water shrew (*Sorex palustris*) are, in fact, both able to “sniff” underwater by blowing bubbles on the substrate and quickly reinhaling them, providing a mechanism for mammalian olfaction underwater (Catania 2006). It is worth emphasizing, however, that water-breathing aquatic animals do not necessarily require a fluid carrier to sense hydrophobic compounds. Indeed, they are able to detect insoluble compounds, distributed in nature as illustrated in Figures 1A and 1D, by the direct tactile contact with their chemosensory organs. But this goes beyond any chemosensory dichotomy based on spatial criteria.

TWO-DIMENSIONAL CHEMOTACTILE PERCEPTIONS

In terrestrial vertebrates, smells can stimulate appetite long before food intake (Boesveldt and de Graaf 2017). In fact, olfaction

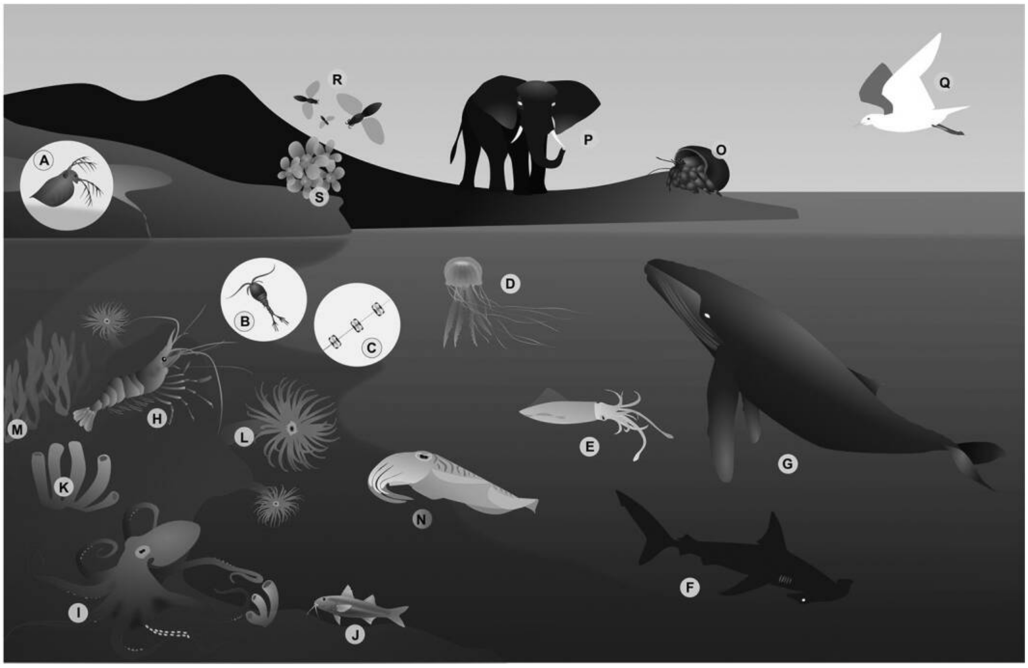

FIGURE 2. SPECIES DISTRIBUTION IN HETEROGENEOUS CHEMOSENSORY HABITATS

According to their lifestyle and habitat, animals are differentially exposed to chemosensory molecules in keeping with their spatial distributions illustrated in Figure 1. In aquatic environments, planktonic crustaceans as *Daphnia* (A) and *Eurytemora* (B), microalgae as *Thalassiosira* (C), and jellyfish (D), squids (E), sharks (F), and whales (G) live in the pelagic zone where waterborne compounds represent the predominant chemosensory distance cues and generate three-dimensional gradients of concentration. However, pelagic animals also encounter hydrophobic cues when they come into contact with other organisms and especially when potential food enters their mouth. In the benthic dominion, instead, shrimp (H), octopuses (I), and mullets (J) live in close relationship with the substrate. They explore by touch a two-dimensional chemosensory space encountering a vast variety of insoluble chemical signals. They are especially emitted by sessile organisms such as sponges (K), cnidarians (L), and algae (M), which are permanently attached to the sea bottom and rely on defensive chemical weapons to prevent predation. Benthic animals also sense waterborne cues, but do not chase them by navigating the water column. Cuttlefish (N), instead, has an intermediate benthopelagic lifestyle, often navigating in the three-dimensional space. Many of the chemical signals perceived by both pelagic and benthic aquatic animals also occur on land, where their two- and three-dimensional spatial distributions can substantially differ, being conditioned by volatility rather than by solubility in water. Among terrestrial animals, hermit crabs (O) and elephants (P) are able to detect chemosensory cues dispersed in air, but cannot navigate in the aerial medium. Instead, seabirds (Q) and insects (R) can fly toward the emitter of airborne foraging cues. This latter response is a way by which flowering plants (S) attract their pollinators. However, when they came into direct contact with potential food sources, all terrestrial animals also sense by "touch" chemical cues that are not volatile. See the online edition for a color version of this figure.

not only contributes, together with taste, to flavor discrimination, but especially assists in navigation by assessing odorant distributions in time and space, and provides information that is required for locating predators, food, or mating partners. In a sense, olfaction performs a function similar to that of sight and hearing, with the difference that it helps to detect molecules instead of light or sound. Accordingly, variability in the size of the olfactory bulb in vertebrates has been explained by the so-called "olfactory spatial hypothesis," proposing that the primary function of olfaction is indeed navigation, with anatomical differences being associated with variability in navigational demand (Jacobs 2012).

According to this position, which is also consistent with the idea that "[s]mell and taste are functional concepts" (Atema 2018:485), olfaction specifically assists in navigation, both in aquatic and terrestrial environments, by detecting waterborne and airborne cues, respectively. Conversely, taste can only provide information about food material that comes into direct contact with receptors in the mouth (Hemilä and Reuter 2008; Boesveldt and de Graaf 2017). As we have already discussed, this position is not universally valid. It is worth noting, however, that many animals can follow chemosensory signals not only within either airborne (Engman et al. 2020) or waterborne (De Lange et al. 2005) plumes, but also by following traces adherent to the substrate by using chemotactile organs such as barbels, oral tentacles, and other cutaneous outgrowths (Mollo et al. 2017). This is particularly evident in marine benthic animals that evaluate potential food sources by detecting compounds adherent to the solid substrate or to the surface of their prey. Chemotactile navigation is crucial for fish species that explore the marine substrate, following hydrophobic traces with their barbels (e.g., mullets, Figure 2J), and for benthic mollusks able to track gradients of appetitive chemotactile stimuli and to recognize and avoid potentially dangerous stimuli (Yafremava et al. 2007; Mollo et al. 2014). Contact perceptions, those definitely associated to taste in humans, can thus provide information useful to locate distant objects as well, although within a two-dimensional space. This evidently undermines spatial taste-smell differentiation, but also has critical implications when approaching the study of chemically mediated ecological interactions such as defense against predators, communication with conspecifics, and the search for food sources in both aquatic and terrestrial environments. There is plenty of evidence, in fact, that both terrestrial and aquatic organisms move on a two-dimensional chemosensory "patchwork" and make choices crucially important to survival by sensing chemicals that adhere to the substrate (Mollo et al. 2017). For example:

- defensive chemical cues can be airborne, waterborne, or surface-adsorbed, or can act directly in the mouth of predators (Wheeler et al. 1964; Krug 2006; Carbone et al. 2013; Giordano et al. 2017);
- chemotactile information plays a central role in ants' social interaction, navigation, and resource exploitation (Riveros et al. 2021);
- bumble bees discriminate between foods of different concentrations by means of chemotactile perceptions (Ruedenauer et al. 2015);
- in the sea slug *Pleurobranchaea californica*, the function of the olfactory bulb is performed in the in the peripheral nervous system of a chemotactile oral veil (Gillette and Brown 2015);
- octopuses (Figure 2I) use specialized chemotactile sensory receptors on their arms to sense several poorly soluble natural products (van Giesen et al. 2020), especially terpenes, which occur in a large variety on benthic substrates. It is worth mentioning that the renowned intelligence of the octopus is actually accompanied by its high ability to perceive and integrate sensory information from the environment (Mollo et al. 2019) and that, during food choice, the octopus turned out to be more dependent on chemical cues than visual ones (Maselli et al. 2020). Accordingly, octopuses have about 10,000 chemoreceptor cells in each sucker, while only about 100 of these cells are present in each sucker of cuttlefish (Figure 2N; Graziadei 1964a,b), which forage above the substrate. Chemoreceptor neurons are even simpler in visually oriented and more active squids (Emery 1975) that are adapted to pelagic life (Figure 2E);
- communication with conspecifics by means of pheromones can be mediated by chemical cues that can be either volatile or nonvolatile, either soluble or insoluble in water, or either detected at a distance or by contact (Mutis et al. 2009; Wyatt 2014, 2015; Thoß et al. 2019; Chung-Davidson et al. 2020);
- wolf spiders use female chemotactile cues as indicators of potential risks and this affects subsequent male courtship behaviors (Moskalik and Uetz 2011), while web-based chemotactile cues also influence male courtship in the black widow spider (Johnson et al. 2011); and
- pheromones secreted by some sea slug species induce an alarm response in trail-following conspecifics (Sleeper et al. 1980; Cimino et al. 1991).

The emerging complexity of the spatial range of chemical communication indicates that, beyond a sharp and unnatural differentiation between taste and smell based on spatial criteria, greater attention to the kind of chemical information helping many species across taxa to find food and mates, and to select habitat, could significantly contribute to outlining realistic scenarios for the heterogeneous species distribution in nature.

MOLECULAR DIFFERENTIATION

ANTHROPOMORPHIC BIAS AND ITS EVOLUTIONARY IMPLICATIONS

The human ability to discriminate between airborne and waterborne stimuli can be extended to other air-breathing animals, but it certainly does not apply to water-breathing animals. Accordingly, it has been proposed that new demands on chemosensory systems dramatically arose during the water-land transition, since the olfactory stimuli changed from hydrophilic to mainly hydrophobic and airborne compounds (Krång et al. 2012). In this view, "[t]errestrial vertebrates were given the 'evolutionary option' to sense odorants that were volatile and not soluble in water" (Tierney 2015:547). This position implies that both the complex biosynthetic pathways required for the production of volatile compounds, and the extremely complex combinatorial coding that characterize olfactory perceptions mediated by odorant receptors (ORs), suddenly appeared on land (Figure 3A, Scenario A). Conversely, a vast literature on marine natural products suggests that, before incidentally becoming airborne on land, many small molecules already played a key role in chemical communication in aquatic systems. Actually, volatile and hydrophobic terpenoids from extant land plants, representing the most abundant group of biogenic volatile organic compounds (BVOCs) in the atmosphere (Peñuelas and Staudt 2010), occur and are detected in aquatic environments as well (Mollo et al. 2017). These signals characterize a kind of complex language mediating crucial ecological interactions (Peñuelas et al. 1995), both in aquatic and terrestrial ecosystems (Mollo et al. 2014, 2017). The same applies to volatile aldehydes of terrestrial plants that are almost insoluble in water and are also produced by marine diatoms (Figure 2C; Pohnert 2000; d'Ippolito et al. 2002, 2003; Adelfi et al. 2019). In parallel, comparative genomic and phylogenetic studies support that chemosensory receptors have been conserved across aquatic and terrestrial taxa, and that OR genes orthologous to those present in mammals, evolved in marine environments prior to the appearance of the earliest vertebrates (Figure 3A, Scenario B; Putnam et al. 2007, 2008; Churcher and Taylor 2009, 2011).

INDISCERNIBILITY OF THE CHEMICAL SENSES AT THE INTERMOLECULAR DISTANCE

The fluid medium (air or water) in which chemical signals are dispersed affects the distance range of chemical communication not only at relatively large spatial scales, as in the case of the navigation of birds and pelagic fish, but also at a microscopic scale, as in bacterial chemotaxis. Complex aqueous media covering chemosensory cells and organs can also considerably influence the approach of the ligands to the receptors. The mucus and the saliva of vertebrates, as well as the sensillar lymph of invertebrates, can have a crucial impact in this phase, requiring the action of soluble carriers to bring hydrophobic ligands into contact with chemosensory receptors. In the end, however, chemical cues must always come into contact with molecular receptors to finally trigger chemosensory perception, so that there is no action at a distance in the ligand-receptor recognition step (Mollo et al. 2017). Consequently, one might ask whether it would be better to adopt the idea that a single chemosensory modality actually underlies the detection of chemical signals coming from distances that can vary according to a wide range of environmental and physicochemical conditions. However, another question remains: Are taste and smell different senses because they involve different molecules?

TOWARD A UNIFYING THEORY ACROSS LIGANDS AND RECEPTORS

Taste and smell are "chemical senses." Accordingly, one might reasonably argue that

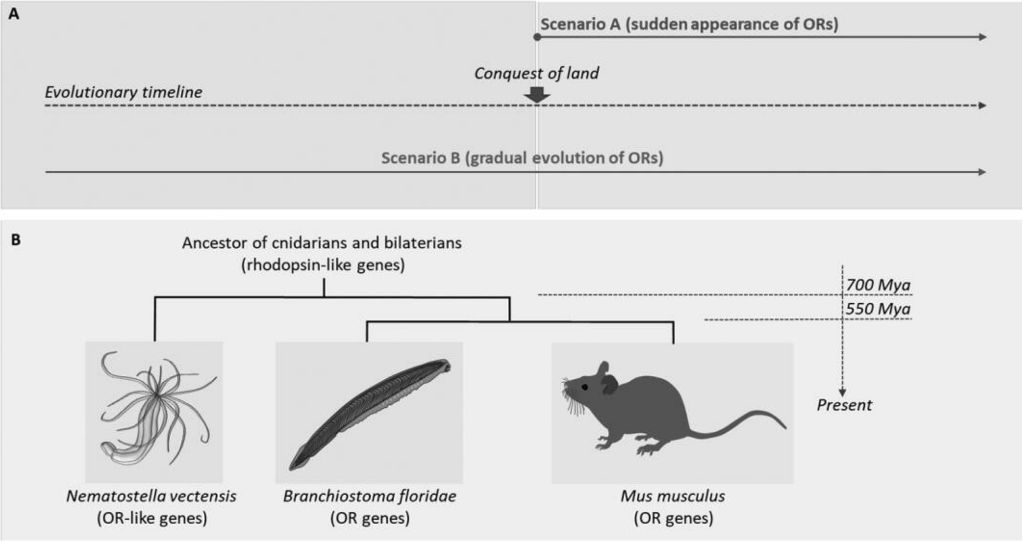

FIGURE 3. SALTATIONAL VERSUS GRADUAL EVOLUTION OF ODORANT RECEPTORS

The hypothesis that dramatic changes in olfactory systems allowed terrestrial animals to sense volatile/hydrophobic cues (Krång et al. 2012) and that "[t]errestrial vertebrates were given the 'evolutionary option' to sense odorants that were volatile and not soluble in water" (Tierney 2015:547) is only justified if these kinds of molecules are distributed on land only. Volatile/hydrophobic molecules are instead widely distributed in aquatic ecosystems (Mollo et al. 2014, 2017; Giordano et al. 2017). In parallel, an evolutionary scenario implying the "sudden" appearance of ORs after the conquest of land (Scenario A) is implausible (Mollo et al. 2014). Indeed, studies in molecular phylogenetics on the rhodopsin-like family of GPCRs (B) indicate that genes from the sea anemone *Nematostella vectensis* and the marine cephalochordate *Branchiostoma floridae* are orthologous to vertebrate OR genes, forming a monophyletic clade (Churcher and Taylor 2009, 2011). Consequently, chordate ORs most likely evolved from a clade of rhodopsin-like genes present in the ancestor of cnidarians and bilaterians (Churcher and Taylor 2011), while vertebrate ORs evolved prior to the split between cephalochordates and chordates (Churcher and Taylor 2009). Approximate divergence dates are expressed in million years ago (*Mya*), according to Putnam et al. (2007, 2008). A gradual evolutionary trend is thus proposed here (Scenario B), supporting that the evolution of ORs continued without interruption during the transition from aquatic to terrestrial life. See the online edition for a color version of this figure.

the difference between the two chemosensory modalities must entail the structures of molecules interacting with specific chemosensory proteins. The universality of such a distinction based on chemical features is, however, definitely falsified by the existence in nature of chemosensory compounds that simultaneously trigger olfactory, gustatory, and chemesthetic sensations (examples in Figure 4). This implies that the terms "smell" and "taste," being applicable to the same concrete chemical objects, actually lose their significance.

Once the universal sensory specificity of ligands has been falsified, the classification of their macromolecular counterparts, the chemosensory receptors, whose specific function is inextricably linked to diagnostic chemical stimuli, also becomes impracticable. In addition, it is worth mentioning that molecular receptors have coevolved with an enormous variety of natural products, which are produced by both unicellular and multicellular species through an equally vast variety of biosynthetic pathways, within a dynamic evolutionary history. This biosynthetic "profligacy" demands a high energy expenditure that is, however, justified by the critical roles played by chemical cues in fundamental biological processes. Whether or not chemosensory receptors have driven the evolution of ligands or vice versa, their specific interactions gradually evolved within and throughout a vast variety of biotic and abiotic conditions.

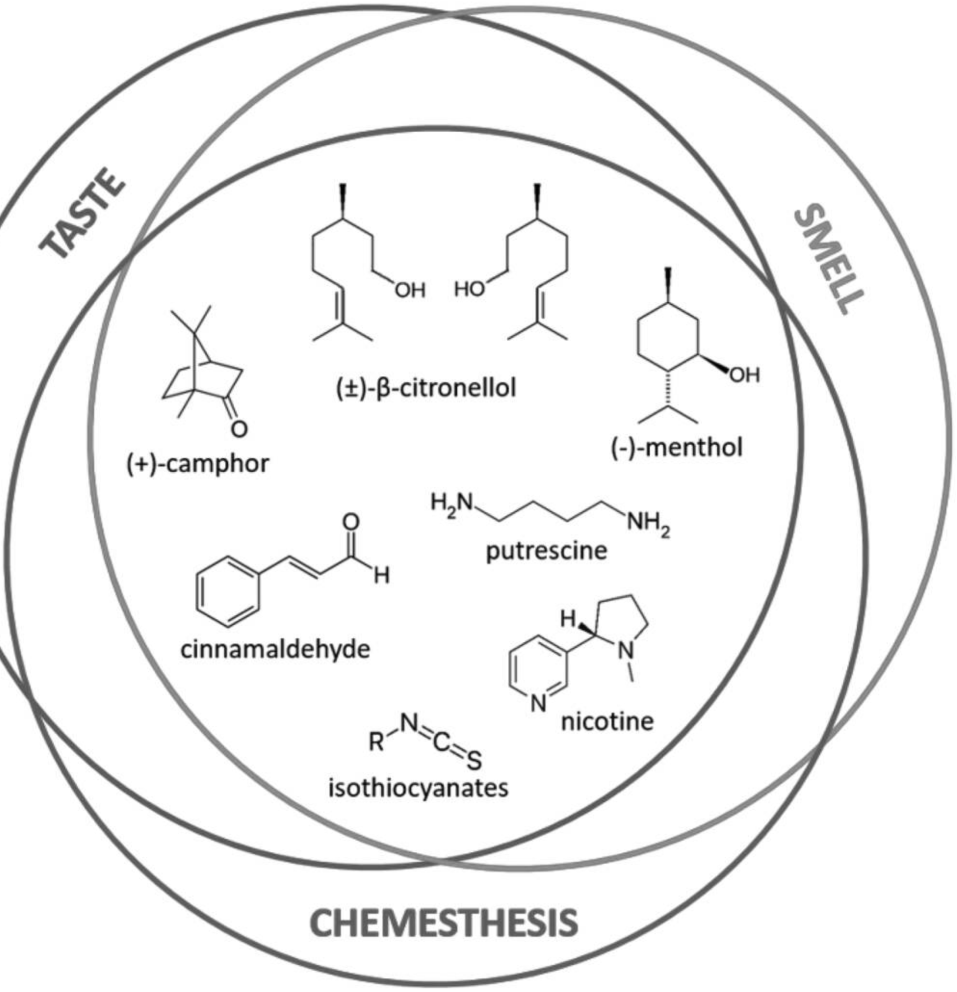

Figure 4. Molecules Detected By Multiple Chemosensory Systems: Each of the Chemicals Shown Is Known to Cause Gustatory, Olfactory, and Trigeminal/Chemesthetic Sensations

The alcoholic monoterpene citronellol has both a fresh floral smell and a bitter or sweet taste depending on its stereochemistry. Cinnamaldehyde is responsible for both the typical taste and smell of cinnamon. Camphor has both a bitter taste and an aversive smell to flies (National Center for Biotechnology Information 2005a; Zhang et al. 2013). Menthol produces a minty smell and a moderate bitterness (Green and Schullery 2003; National Center for Biotechnology Information 2005b) but also affects the sensitivity of gustatory receptors to stimulation by other cues (Lundy and Contreras 1993). Polyamines, such as putrescine, which is responsible for the foul odor of putrefying flesh, also induce multimodal taste sensations (National Center for Biotechnology Information 2004a; Hussain et al. 2016). Isothiocyanates contribute to both the taste and odor of Brassicaceae (National Center for Biotechnology Information 2005c; Wieczorek et al. 2018; Matsunaga et al. 2019), interacting with both taste and odorant receptors. The alkaloid nicotine activates: the taste system via taste receptors and downstream effectors that are common to sensing sweetness, bitterness, and umami; the nicotinic acetylcholine receptors; and the canonical olfactory pathway (National Center for Biotechnology Information 2004b; Oliveira-Maia et al. 2009; Bryant et al. 2010). All molecules listed above also activate TRP ion channels that cannot be unambiguously classified within taste or smell sensory systems, occurring in epithelial cells in both the nose and tongue (Jordt et al. 2004; Al-Anzi et al. 2006; Lin et al. 2008; Gewehr et al. 2011; Alpizar et al. 2013; Ortar et al. 2014; Wieczorek et al. 2018) as well as in extraoral organs (Cheng 2018). This difficulty in classification has led to the creation of a new ad hoc sense, indicated as "chemesthesis" or trigeminal sense, responsible for the pungency, thermal sensation, and pain produced by hot chili peppers (Lundström et al. 2011). Indeed, the archetypal member of the family of TRP channels, the transient receptor potential vanilloid subtype 1 (TRPV1), is activated by capsaicin (Tominaga 2005; Pingle et al. 2007; Aroke et al. 2020), the pungent component of peppers. Chemesthesis is considered the third chemical sense involved in human eating and drinking behaviors (Green 1996; Kadowaki 2015). See the online edition for a color version of this figure.

A large part of this evolutionary trend took place in aquatic environments but continued without interruption during the transition from aquatic to terrestrial life (Figure 3A, Scenario B). Combined with the gradual evolution of molecular interactions, shifts of function also occurred. This is confirmed by the highly diversified functions of chemical signaling in extant species. On one hand, it has been speculated that hormones acting in chemical communication among different cell types and organs within the same organism represent some of the oldest signaling molecules (Kushiro et al. 2003). On the other hand, several hormones are terpenoid derivatives, as are most hydrophobic chemicals acting as mediators of a variety of ecological interactions in marine and terrestrial habitats. Hormones lie outside a taste-smell schematization (Foster et al. 2014), although their receptors, which are highly specific toward their endogenous ligands, can be also responsive to chemically distinct exogenous agents, including endocrine-disrupting chemicals and natural compounds involved in exteroception. Accordingly, the ligand-binding domain of the estrogen receptor alpha (ERα) shows a structural architecture very similar to bacterial taxis receptors (Lakshmanan Mangalath and Hassan Mohammed 2021).

In support of the idea that ORs and taste receptors (TRs) do not act as selective mediators of smell and taste, respectively, it is worth recalling that they are not only expressed in nasal and oral cells. This ectopic expression of chemosensory receptors is associated with a variety of functions, including sperm chemotaxis, wound healing, hair growth, muscle regeneration, cancer cell inhibition, adiposity, hormone release, and innate immunity (Lee et al. 2019). The remarkable diversification in the location, distribution, and function of chemosensory receptors across taxa has been often highlighted in the literature, where it has been shown that:

- ORs and TRs, both belonging to the large family of G-protein-coupled receptors (GPCRs), as well as transient receptor potential (TRP) ion channels, are expressed in a wide range of tissues, including in “nonsensory” inner organs (Kadowaki 2015; Dalesio et al. 2018; Weidinger et al. 2021), implying that the restricted perception of these receptors as mere mediators of smell and taste is “outdated” (Foster et al. 2014);
- ORs have been found to be expressed in mammalian “taste” cells, raising the “intriguing possibility that taste and olfaction might overlap more than previously thought” (Malik et al. 2019:298);
- insect ORs, which are characterized by an inverted direction of membrane insertion compared to vertebrate GPCRs, are functional in true taste neurons of *Drosophila*, producing responses to smells that are similar to those obtained with tastes (Hiroi et al. 2008);
- ionotropic receptors (IRs) have been discovered in *Drosophila melanogaster* (Benton et al. 2009) as variants of the ionotropic glutamate receptors (iGluRs), representing a class of receptors that only evolved within invertebrates (Croset et al. 2010; Wicher and Miazzi 2021). Although iGluRs mediate neuronal communication at synapses throughout vertebrate and invertebrate nervous systems (Gereau and Swanson 2008), IRs are expressed in invertebrate chemosensory organs and have several tuning modalities, which cannot be defined as “taste” or “olfaction” (Ai et al. 2010; Silbering et al. 2011; Rytz et al. 2013; Hussain et al. 2016; Frank et al. 2017; Knecht et al. 2017). IRs are, in fact, associated with a variety of sensory functions, including taste, olfaction, thermosensation, and hygrosensation (Eyun et al. 2017; van Giesen and Garrity 2017). Moreover, IRs are also expressed in the dorsal organ cool cells of *Drosophila*, where they are involved in cool avoidance behaviors (Ni et al. 2016);
- along with IRs, olfactory sensory neurons of insects express gustatory receptors (GRs) responding to CO_2 (Kwon et al. 2007);
- polyamines are transported by both air and water, occurring in nature within the distribution illustrated in Figure 1C. Chemosensation of polyamines in insects is mediated by IRs (Silbering et al. 2011; Hussain et al. 2016), while in both aquatic and terrestrial vertebrates, these compounds are detected by a further group of GPCRs, the trace amine-associated receptors (TAARs; Borowsky et al. 2001; Hussain et al. 2013). However, the study of available RNA-Seq data from human tissues has led to an appreciation of the ectopic expression of TAARs, especially in the ovary and testis (Flegel et al. 2013);

- soluble proteins are concentrated in olfactory organs of vertebrates and invertebrates and seem to be involved in the delivery of hydrophobic molecules to membrane chemosensory receptors by crossing the aqueous layer covering chemosensory neurons. Among them, odorant-binding proteins (OBPs) are produced in both the olfactory and gustatory sensilla of *Drosophila* and are involved in the transport of both hydrophobic odorant and bitter tastant molecules (Swarup et al. 2014); and
- neither insect ORs nor OBPs are universally distributed in terrestrial arthropods and may be absent in aquatic crustaceans. In particular, they were not found in two planktonic crustaceans, the freshwater cladoceran *Daphnia pulex* (Peñalva-Arana et al. 2009; Figure 2A) and the marine copepod *Eurytemora affinis* (Eyun et al. 2017; Figure 2B). IRs with multiple sensory functions, which are the most dominant chemosensory proteins in crustaceans, outnumbering TRP channels and gustatory receptor-like receptors (Kozma et al. 2020), allow these aquatic animals to sense volatile/hydrophobic molecules as well.

Precisely the complexity and diversity of the different chemosensory systems, and families of chemoreceptors, prevent a sharp differentiation of the chemical senses that, on those categories, individually taken, should be founded. In principle, each different type of ligand, or receptor, or molecular interaction, or even their anatomical or phyletic distribution can be used to define a new chemical sense, for which we could coin a new name. What has been done for the capsaicin receptor and the so-called "chemesthesis" or "trigeminal sense" could be actually applied to define a huge number of different chemical senses.

ANATOMICAL AND NEUROBIOLOGICAL DIFFERENTIATION

TOWARD A UNIFYING THEORY ACROSS ORGANS AND NEUROPHYSIOLOGICAL SYSTEMS

At the anatomical level, the taste buds on our tongues are the primary organs of taste, and the olfactory epithelium at the back of the nasal cavity is responsible for detecting odors. This distinction, however, cannot include the vast variety of chemosensory systems in the animal kingdom. Aristotle himself already argued that "the organ of smell just is whatever part of its body an organism uses to perceive odour" (Johnstone 2012: 166). The evolution and diversification of complex organs is, however, a gradual and cumulative process. Accordingly, Charles Darwin stated: "If it could be demonstrated that any complex organ existed, which could not possibly have been formed by numerous, successive, slight modifications, my theory would absolutely break down. But I can find out no such case" (Darwin 1859:189). Therefore, it should not be surprising that single-celled organisms contain simple but already efficient sensory structures. This is particularly evident in the case of vision, with a functional eye-like "ocelloid" in dinoflagellates (Gavelis et al. 2015) and in the case of cyanobacteria that seem to "have what it takes to qualify for the most basic definition of vision" (Nilsson and Colley 2016:R369). There is evidence that the senses of touch and hearing also originated in unicellular organisms (Lumpkin et al. 2010; Exbrayat and Brun 2019). Conversely, in the case of chemosensation it has been proposed that the sense of smell "is more correctly defined by the neural system used" (Kamio and Derby 2017:517), implying that olfaction evolved after transition to multicellularity. Actually, such a definition of olfaction opposes a gradual evolution of the olfactory systems across phylogeny, neglecting the important similarities of cell membrane structure and function in aneural and neural systems, which have long been emphasized to underlie related neurobiological phenomena (Eisenstein 1975). In favor of a gradual evolution of olfaction, it has been recently found that the ancestral orthologs of the synaptic genes involved in the fundamental way neurons communicate are present in multiple aneural organisms (Viscardi et al. 2021). In parallel, relevant studies have clarified that both olfactory and gustatory abilities in multicellular organisms (as well as chemosensory learning abilities) have evolved from forms of life not equipped with complex neuronal networks. In particular:

- prokaryotes have been proposed as model systems for understanding the evolution of olfactory and gustatory systems in higher organisms. Actually, bacteria respond to volatile chemical gradients (Nijland and Burgess 2010), but also utilize contact-dependent signaling (Blango and Mulvey 2009);

- an unmistakable form of chemosensory learning has been demonstrated in the unicellular but multinucleated eukaryote *Physarum polycephalum* (the true slime mold; Boisseau et al. 2016); and
- comparative structural analyses of both odorant and gustatory receptors in insects, unicellular eukaryotes, and plants indicate a common origin of these proteins in the last common eukaryotic ancestor (Benton 2015; Benton et al. 2020).

Chemosensation is, however, not always mediated by complex neural systems even in humans. Responding to chemotactic gradients with directed cellular migration is, in fact, also a feature of single human immune cells (Thomas et al. 2018). Even human spermatozoa are attracted by bourgeonal (an aromatic aldehyde) that can be smelled by the nose (Vosshall 2004). This also applies to sperm attractants affecting the reproductive behavior of many other animals, including marine cnidarians (Miller 1979; Coll et al. 1995), as well as to pathogen-associated molecular patterns inducing a chemotactic response in earthworm coelomocytes (Daly et al. 2017). Of course, whether innate or adaptive, these sensory perceptions cannot be classified as olfactory or gustatory phenomena based on the specific neural systems employed. On the other hand, when considering multicellular organisms, an evident functional promiscuity emerges in the study of anatomical and neurophysiological structures. For example,

- the sensory sensilla on the mouth parts of insects are involved in both gustatory and olfactory functions (Rana and Mohankumar 2017; Ruschioni et al. 2019);
- electrophysiological recordings indicate that *Drosophila* taste neurons also respond to odor ligands (Hiroi et al. 2008);
- bimodal neurons respond to both gustatory and olfactory stimuli in rats (Samuelsen and Fontanini 2017);
- the vomeronasal organ (VNO), which is specifically discussed in the next section, is a structure supporting the accessory chemosensory modality of "vomerolfaction," which involves the detection of both volatile and nonvolatile chemical cues;
- the tongues of snakes facilitate the access to vomerolfaction by bringing both airborne and nonvolatile chemical stimuli to the VNO (Kubie and Halpern 1975; Halpern and Kubie 1980; Ache and Young 2005; Daghfous et al. 2012);
- histological observations indicate a close interaction between taste buds and the VNO (Schmidt and Wöhrmann-Repenning 2004);
- the nose-tapping behavior in plethodontid salamanders allows pheromone recognition by bringing nasolabial grooves into contact with marked substrates (Graves 1994); and
- secondarily aquatic mammals, such as dolphins, seem to perceive orally both tastes and what other mammals perceive by smell (Kremers et al. 2016).

IS VOMEROLFACTION A DIFFERENT SENSE?

VNO is enclosed in a capsule on the anterior nasal septum of mammals (Dulac and Torello 2003), allowing detection of chemicals collectively called "vomodors" (Cooper and Burghardt 1990). These chemical cues mainly interact with specific G-protein-coupled receptors, the type-1 vomeronasal receptors (V1Rs; Dulac and Axel 1995) and the type-2 vomeronasal receptors (V2Rs; Herrada and Dulac 1997; Matsunami and Buck 1997; Ryba and Tirindelli 1997). Although the concept of vomerolfaction is per se linked to the presence of the VNO, both V1Rs and V2Rs have been also found in fish that do not have this organ (Grus and Zhang 2009). Indeed, a comparative analysis between the olfactory transcriptome of *Danio rerio* (zebrafish) and mouse revealed a high degree of molecular conservation, indicating that "the molecular and cellular mechanisms underpinning olfaction in teleosts and mammals are similar despite 430 million years of evolutionary divergence" (Saraiva et al. 2015:1). Recently, it has also been shown that the chemosensory receptor repertoire of *Scyliorhinus canicula*, the catshark, is dominated by V2Rs (Sharma et al. 2019). Variations in the number of different vomeronasal genes across taxa seem to reflect adaptations to terrestrial or aquatic lifestyles (Shi and Zhang 2007). Accordingly, V1Rs bind small airborne compounds (Boschat et al. 2002; Del Punta et al. 2002), while V2Rs mediate detection of large water-soluble molecules (Leinders-Zufall et al. 2009; Haga et al. 2010). In spite of this, however, the above findings conflict with the idea that a special chemosensory modality is strictly associated to the VNO, with its specific function. Accordingly, it is worth mentioning that:

- VNO receptors can be ectopically expressed in the main olfactory epithelium of mammals, while certain ORs are also expressed in vomeronasal neurons (Rodriguez et al. 2000);
- the VNO is also known to contain formyl peptide receptors (FPRs), which are not only involved in chemotaxis, but also have roles in homeostasis of organ functions, and modulation of inflammation (Rivière et al. 2009);
- the VNO is not only involved in the identification of pheromones, but also in mediating interspecies defensive and feeding behaviors (Halpern and Martınez-Marcos 2003; Papes et al. 2010);
- the VNO has no obvious function in humans, where pheromonal communication seems to be conveyed via the main olfactory system (Frasnelli et al. 2011); and
- histological observations indicate a close interaction between taste buds and the VNO (Schmidt and Wöhrmann-Repenning 2004).

HOLISTIC FLAVORS

When focusing on humans and other vertebrates, it has long been clarified that gustatory and olfactory cells respond to chemical stimuli by generating impulses that travel along gustatory or olfactory nerves to specific processing areas in the cerebral cortex. However, a convergence of taste and smell information in flavor perception has been proposed to occur in the anterior insula, operculum, ventrolateral prefrontal cortex, and the orbitofrontal cortex (de Araujo et al. 2003; McCabe and Rolls 2007; Seubert et al. 2015) This convergence has been recently supported by dynamic causal modeling demonstrating an effective connectivity, integration, and synergy of taste and smell in the human brain at anterior insula and rolandic operculum (Suen et al. 2021). This is consistent with studies on associative learning that shows how odors take on taste qualities, reflecting the central integration of odors and tastes into flavors (Prescott et al. 2004). Actually, such a chemosensory synergy not only contributes in determining the palatability of food, but also induces combined emotions by activating the same areas of the limbic system, recalling memory associations about the reward value of the consumed item. Consequently, in addition to the issues discussed in previous sections about the taste-smell differentiation based on spatial criteria, the central convergence of taste and smell into a "holistic flavor experience" (Seubert et al. 2015:1662) also undermines the special role of taste in evaluating food palatability.

Is It Only a Matter of Semantics?

From all of the above arguments it emerges that both single cells and multicellular organisms use a variety of molecular, anatomical, and physiological systems to carry out fundamental activities for survival, mediating inter- and intraspecific communication over long and short distances, as well as by contact. This results from the continuous adaptation, over long periods of time, to environmental factors and biotic interactions. However, in spite of such an intricate diversification, it is still possible to preserve a sharp differentiation of the chemical senses, and the related terminology, but at the cost of anthropomorphizing biology and evolution regardless of how much this may hamper research on the chemosensory world. Actually, this is what is currently happening in science, favoring the spread of a variety of prejudices and oversimplifications. The following are a few examples from a vast biased literature:

- Researchers loyal to the traditional view that olfaction is a distance sense continue to consider only waterborne stimuli when studying underwater olfaction. Their choice is based on the idea that aquatic organisms especially sense water-soluble chemicals since they cannot encounter airborne, volatile odorants (Ache and Young 2005; Caprio and Derby 2008; Scott 2008; Krång et al. 2012; Tierney 2015). However, they neglect that chemotactile navigation, oriented by following hydrophobic traces adhering to the substrate, is also crucial for many aquatic species to locate distant objects (Mollo et al. 2017).

- Since α-amino acids and other waterborne cues are considered major "olfactory" stimuli perceived by sharks at a distance (Meredith and Kajiura 2010; Figure 2F), shark species have been ambiguously called "swimming noses" (Yopak et al. 2015). Reasonably, instead, waterborne compounds are detected by the shark's molecular receptors of taste, which are well conserved from fish to terrestrial vertebrates (Oike et al. 2007; Bachmanov et al. 2014; Morais 2017; Amodeo et al. 2018). Conversely, it has been even claimed that in aquatic animals "all chemicals sensed are in aqueous solution, and strictly all chemoreception should be termed 'taste'" (Rebora et al. 2019:147). Once again, both the above positions overlook the notion that aquatic animals are also able to perceive hydrophobic cues when they come into contact with chemosensory receptors in the mouth or in chemotactile appendages (Mollo et al. 2017).
- The Orco protein is coexpressed with insect olfactory receptors (Sato et al. 2008; Mukunda et al. 2014; Cattaneo et al. 2017), and is thought to have evolved from within the gustatory receptor gene family (Robertson 2019; Thoma et al. 2019). All currently known and functionally characterized insect Orcos bind a nonvolatile and hydrophobic compound, the synthetic agonist VUAA1 (Jones et al. 2011), but natural ligands of Orco have not yet been identified. The existence of natural chemosensory molecules with physicochemical features similar to VUAA1 could be reasonably conceived and found in nature among compounds with the spatial distribution shown in Figure 1D. But this will come with the cost of "reforming the illusion" that the involved receptor proteins are olfactory structures and that olfactory cues must be necessarily airborne or waterborne. For example, many Orco-positive neurons have notably also been found in the antennae and palps of the truly "submarine" larvae of the marine intertidal insect *Clunio marinus*, whose larvae can live for one year, but the adult life span is only a few hours (Missbach et al. 2020). Both air- and waterborne stimuli have been especially considered in the study of the chemosensory adaptations of *C. marinus*, because chemical cues "need to be taken up from different media" (Missbach et al. 2020:12). Thus, chemical cues that are not taken up from the air or from water (Figure 1D) have lamentably been disregarded as possible ligands of *C. marinus* Orco/OR complexes because of prejudice.
- Fish OR genes have been grouped according to the assumption that their corresponding receptors can only detect olfactory waterborne molecules (Niimura and Nei 2005; Niimura 2012), disregarding the real patterns of affinity of the receptors for ligands. Olfactory GPCR genes have thus been artificially separated into receptors for airborne molecules and receptors for waterborne molecules. This position actually neglects that fish can also detect insoluble molecules when possible food enters the mouth or chemotactile organs come into contact with the emitter of the chemical signal. This latter aspect was also not adequately considered as a possible explanation of the "unexpected" presence of functional ORs in fish that are very similar to those present in terrestrial vertebrates (Niimura and Nei 2005; Amemiya et al. 2013; Picone et al. 2014).
- Although OR genes in fish are more diverse than those in mammals, an analysis of the increased number of OR genes in the tetrapod lineage has contributed to the view that olfaction is mainly a terrestrial sense (Niimura 2009, 2012). However, it could be argued that, rather than supporting a greater importance of olfaction on land than in water, the association of increasing OR gene number with decreasing OR gene diversity suggests a preponderant role for signal amplification among different possible fates of gene duplication (Zhang 2003). In this view, OR signal amplification (i.e., the immediate effect of gene duplication) implies an increased sensitivity to smell (Kondrashov 2012). Thus, duplications most likely first acted as a mechanism of adaptation to the extreme rarefaction of aerial volatile/hydrophobic cues. This mechanism would have represented an important transitional step, because the same chemosensory molecules were already detected, but at much higher concentrations, in the aquatic environment. Actually,

hydrophobic compounds are highly concentrated on the surfaces of many extant benthic organisms, such as sessile sponges, cnidarians, or mollusks, in their mucous secretions, and on the substrates on which they live (Mollo et al. 2014, 2017; Giordano et al. 2017). Many of these molecules are, instead, quite rarefied in the air (Mollo et al. 2014). Positive selection should have thus favored the long-term persistence of OR gene duplications, ensuring the detection of astonishingly low concentrations of volatile chemosensory signals by terrestrial animals. This trend neither affected the complex combinatorial recognition pattern of the stimuli, nor required the dramatic evolution of new kinds of receptors during the water-land transition (Figure 3). In this view, the emerging model is characterized by both higher probability and lower discontinuity than the aforementioned theories requiring a "sudden" evolution of smell on land. Therefore, a plausible evolutionary scenario envisages the structural and functional conservation of "aquatic" chemosensory receptors in semiaquatic species with limited mobility on Earth. The gradual amplification of the signals by gene duplication has then set the stage for adaptations in the mechanisms of breathing and locomotion on land, progressively matching enhanced sensitivity to extremely diluted signals with increased range of action in reproduction, defense, and food capture.

Does Philosophy Need Science?

The belief that taste and smell are different senses has prevailed since antiquity. The theme was already debated by ancient Greek philosophers, and especially by Aristotle in his theory of the senses, where taste and smell are thought to differ in terms of both their spatial range (Sorabji 1971) and their proper "objects" (Johnstone 2012). Philosophically musing with senses, Aristotle argued that all smelling must be done at a distance from the object smelled, while what is perceived by taste is directly contacted (Sorabji 1971). This spatial differentiation has remained substantially unmodified over time among philosophers, with smells still considered as spatially extended (O'Callaghan 2016) and coming from some direction and distance (Aasen 2019). On the other hand, Aristotle also stated that "[t]wo senses are different if they have different proper objects and two senses are the same if they have the same proper object" (Johansen 1996:11). Although an ontological controversy is still alive in modern philosophy to define odors as "objects" or "features" (Skrzypulec 2019), it is worth considering that in Aristotle's time it was believed that everything was made up of a combination of primary elements (fire, water, air, and earth), which "do not have strict substantial forms, and for this reason they are substances only potentially" (Sokolowski 1970:265). In such prescientific conditions there were no tools to differentiate sensory systems, objects, and stimuli as material entities with specific physicochemical features. Later philosophical studies, up to the contemporary age, especially focused on the representational aspects of senses, treated olfactory objects as mental objects, and sometimes relegated chemical senses to the rank of "lower senses" (Becker 2009; Richardson 2013; Barwich 2019). Actually, only very recently has philosophical research begun to consider that both taste and smell register chemical properties (Korsmeyer 2019), and a "molecular structure theory" has been offered proposing that "smells are the molecular structures of chemical compounds within odor plumes" (Young 2016: 520). It is worth mentioning, however, that this latter position converges in a spatial definition of olfaction as a distance sense, assuming that odiferous molecules are diffused in "plumes."

From the above, it appears that the arguments proposed in the present article could open intriguing avenues in the relevant philosophical debate. Although it has been recently highlighted that "science needs philosophy," which should be perceived as not antagonist to scientific progress (Laplane et al. 2019), it is also certainly clear that present-day "philosophy must find paths of inquiry and verification that lie within reality as it is conceived today in all its manifestations. This reality, however, can in no instance be genuine and wholly present without science" (Jaspers 1971:13).

Conclusions

Living organisms perceive a vast variety of chemical stimuli, obtaining information on the surrounding world. These molecules are differentially distributed in the environment so that they generate gradients of concentration that can develop in both two- and three-dimensional spaces, depending on specific physicochemical properties. Such gradients provide the detector organism with useful information for identifying and locating the source, and contribute greatly to the characterization of different habitats and chemosensory spaces, favoring a variety of adaptations to perceive, decode, and integrate chemical information. This complexity does not allow for discrimination between two different chemical senses (taste and smell), or four if considering chemesthesis and vomerolfaction, based only on spatial range, the molecules involved, or the anatomical and neurophysiological systems because differentiation implies a misrepresentation of natural conditions. All of the positions that have been adopted to classify different chemosensory perceptions are based on idiosyncratic evidence and cannot be accepted as universal. In particular, the growing evidence of a complex interplay among and between receptors and ligands involved in the detection of chemical and physical stimuli prompts a definitively more interconnected view of the senses.

An analysis of the theoretical and empirical research led us to demonstrate the fallacy of the taste-smell differentiation, which cannot be applied to all forms of life, especially aquatic organisms. We argue that anthropomorphic biases have fostered the neglection of key processes shaping ecological and evolutionary scenarios, thus profoundly hampering our research efforts for a better understanding of the evolution of chemosensation, especially during the transition both from aquatic to terrestrial life, and from single cell to multicellular organisms. This has prompted us to propose the unification of all chemosensory modalities within a comprehensive theoretical framework that opposes the current misleading nomenclature, whose universality is falsified by abundant evidence. Our vision is that there is no taste and no smell in nature, no chemesthesis and no vomerolfaction, but a vast and blurred variety of modes of chemical communication that could be collectively called "chemosensation," which always starts from the interactions between ligands and receptors, two chemical entities both occurring in an immense structural variety in nature.

Perhaps ordinary people, chefs, wine tasters, perfumers, and poets will not need to revise their view on chemical senses, since the taste-smell distinction fits rather well with the human condition and its associated perceptual categorizations. Conversely, biologists strictly need to incorporate information from the study of the entire diversity of living organisms and their ecological interactions when approaching the complex theme of the evolution of chemical communication and especially when designing experimental protocols. A comprehensive approach is, however, hampered by what has become an "epistemological obstacle" pervading the chemosensory literature: the ancient belief that taste and smell are two different senses. Relevant information has been, in fact, extensively misinterpreted according to an anthropomorphic confirmation bias. Following Bachelard's statement: "Intellectual habits that were once useful and healthy can, in the long run, hamper research" (Bachelard 2002:25), the time has come to abandon the differentiation between the chemical senses and start asking better questions about the complex, nuanced, and interconnected manners by which a vast variety of chemicals have become signals crucially important to survival.

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Handling Editor: Liliana M. Dávalos