Chemoreception, olfaction and taste: scientific evidence replaces "*Assays in biopoetry*"

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Taste and olfaction were long considered to be outside the realm of science because of their seemingly subjective nature and lack of end points that could be measured and quantified. According to Galileo, nature is written in "*in lingua matematica, e i caratteri son triangoli, cerchi, ed altre figure geometriche*", and without this numeric connection, research is only "*un aggirarsi vanamente per un oscuro laberinto*".[1] Galileo concluded, on the topic of this special issue, that "*sapori, odori, non sieno altro che puri nomi*", whose physical base is the interaction of "*materie sottili e tenui*" with "*mammillule*" located on the tongue and the nose, where "*son ricevuti I lor toccamenti con nostro gusto o noia*".[2] In other words, the volatility of a compound can be measured by its boiling point, which is science, while its odor is a subjective and unmeasurable trait, alien to science. Four centuries later, we still agree with Galileo that senses, although mediated by the activation of specific sensors, are actually the result of the brain activity that assign, for instance, the pleasant rose note to the vapors emitted by the flower with the same name. On the other hand, we now speak of molecules and not of *materie sottili e tenui*, receptors rather than *mammillule* and interactions rather than *toccamenti*, and the molecular mechanisms underlying sensing can be investigated with the means of modern science. Research on olfaction and taste, once mostly spurred by curiosity for their hedonic connections (perfumery and gastronomy, respectively), is now fully integrated into biomedical research as part of chemoreception, the way living organisms respond to environmental chemical stimuli. Quite remarkably, some of these chemical stimuli turned out to mimic also physical sensations like heat, cold, and pressure, blurring the distinction between chemical and physical senses.[3]

Two seminal discoveries triggered the current intense research in chemoreception. The first one was the identification of specific receptors for olfaction, taste and trigeminality, a term broadly covering the sense of heat and pressure, incidentally already unified in Aristoteles's view of senses.[4] These *mammillule*, mostly metabotropic for taste, metabotropic for olfaction and ionotropic for trigeminality, make it possible to apply the methods of modern pharmacology to the study of chemoreception, a topic discussed in the review by Krohn and colleagues (*Human cell-based taste perception- a bittersweet job for industry*). The second discovery was that chemoreceptors are also expressed ectopically in non-sensory tissues like heart, brain, lungs, testes, sperm and ovaries, where their presence suggests the existence of endogenous ligands, maybe derived from the intestinal microbioma, our inner "environment".[5] If the capsaicin receptor (TRPV1) is a heat sensor, why is it expressed in the central nervous system or in the prostate, where temperature is constant?[3] What do bitter receptor taste and olfactory receptors smell in muscles?[6]

The relevance of chemoreception is highlighted by the role it plays in the most primary event of our life, namely the fecundation of an ovule by a spermatozoon. Spermatozoa were reported to follow a scent trail to locate the ovule, in a veritable cellular version of what Don Giovanni refers to Leporello as "*odor di femmina*" in a night dialogue of Mozart's opera. A specific olfactory receptor (hOR17-4) is highly expressed in sperm, and was supposed to be used to locate the ovule.[7] Since hOR17-4 is sensitive to the odor of lily-of-the-valley (*Convallaria majalis* L.) and its synthetic mimic bourgeonal, this compound was believed to somewhat mimic the bouquet of "odorants" released by the ovule.[7] Later studies showed that the sperm trail to the ovule is actually hormonal, and based on two non-nuclear progesterone receptors, the ion channel CatSper (Sperm-specific cation channel)[8] and the serine protease ABHD2 (α/β hydrolase domain-containing protein 2), an enzyme of the endocannabinoid system.[9] CatSper is sensitive to bourgeonal as well as to a few other odorants, although at much higher concentrations than those of progesterone,[8] while some ABHD-type hydrolases are inhibited by triterpenoids.[10] The sensitivity of these receptors to small molecules and the promiscuous ligand inventory of CatSper suggest that chemotaxis disruptors should be of concern for aquatic wildlife not less than hormonal disruptors, since some fragrance ingredients are stable and long lasting, with bourgeonal being found, for instance, to contaminate the water of Venice canals (too many tourists and too little water exchange).[9] The delicate network of chemical interactions going on in marine life is discussed in the reviews by Mollo and colleagues on '*Taste and smell in aquatic and terrestrial environments*' and by Kamio and Derby on '*Finding food: how marine invertebrates use chemical cues to track and select food'*. There is little doubt that perfumes and cosmetic are confusing marine life, adding insult to the human devastation of the seas.

Despite recent advances that make available receptors and ligands (both agonists and antagonists) for many Galilean *mammillule*, their study is fraught with difficulties. A major one is the lack of appropriate animal models. For instance, most vertebrates including mice use two olfactory systems, the nasal and the vomeronasal systems, but only the first one seems to exist in humans.[12] Also, the function of taste receptors has been tuned by diet, and the human diet is significantly different from those of other vertebrates and even from the diet of our ancestors, at least in the Western world. Bitterness in particular is evolutionary acquired, and continues to evolve. The β-glucopyranoside salicin tastes bitter to humans, but leaves rodent indifferent.[11] Finally, the ectopic expression of chemoreceptors and the reflexes associated to their activation make dangerous to draw conclusions from animal studies. The clinical failure of TRPV1 antagonists , the major drug-discovery project based on chemoreceptors to date, was essentially due to the failure of knock-out animal models to predict the acute hyperthermic effects associated to the block of this ion channel in humans.[3] This underlines the crucial importance of assays with human cell lines as a research tool, as outlined in the review of Krohn and colleagues. On the other hand, studying the animal world continues to be indispensable for deciphering molecular mechanisms triggered by distant vs. contact chemosensation, as outlined in the highlight article on '*Contact chemosensation of phytochemicals by insect herbivores'* by Boland and colleagues and the viewpoint on '*Decoding chemical communication in* *nematodes'* by Butcher. Study of non-model systems also enable scientists to understand how organisms actually interact in the natural world.

The issue of subjectivity is especially relevant for olfaction, the only sense that "travels" via the emotional center of the brain, the limbic system. Odor can, in fact, trigger dramatic responses, as already realized by the ancient historians who recorded the terror of the Roman horses at the odor (and not the sight!) of the elephants of the Sasanian army of Shapur I during the long confrontation of the two Empires in the 3rd century BC.[14] (incidentally, elephants not only have the longest nose within mammals, but also the largest number of olfactory receptors (1948),[15] outsniffing dogs, while their olfactory communication via the monoterpene frontaline has an interesting chirality trait[16])

Other difficulties are related to the mechanisms involved in chemoreception, that are poorly known. Odorants must be volatile, and therefore essentially apolar and of small molecular weight, but, nevertheless, many of them have one single digit picomolar or even lower detection ranges, suggesting the existence of a an additional molecular "glue" to function beyond the simple complementarity of shape and polarity that underlies the lock-and-key model for the interaction of small molecules with macromolecules. Block and colleagues provides strong evidence that this could be metal binding in their contribution '*The role of metals on olfaction*', arguing against the quantum chemistry-based vibrational theory of olfaction.

Finally, the neurophysiological logic of chemoreception is still largely elusive, especially for olfaction. Olfactory receptors are expressed in unique olfactory neuronal cell type in a one-cell-one-receptor logic. On the other hand, most odorant bind a large number of receptors, making the response combinatorial. For an odorant that can activate four receptors (1% of the human portfolio of receptors), the number of possible combinations is astronomical (400!/ (4!) x (396!), that is $>10^{10}$), with an infinite palette of nuances. Conversely, the gustatory system has little discriminating power, and different tastants diverge only for the intensity and not for the quality of the sensation they evoke.

When the geologist Hess resurrected Wegener's theory of the continental drift, he called his seminal 1962 article on the history of ocean basins '*An essay in geopoetry'*, acknowledging the still speculative side of his theory of seafloor spreading (later fully confirmed).[17] In a similar vein, some articles in this issue have a variable but unavoidable trait of "*Assays in biopoetry*" that we hope will stimulate readers attention, and trigger further work in an area where secondary metabolites, as environmental messages, play such a critical role.

References

1 *La filosofia è scritta in questo grandissimo libro che continuamente ci sta aperto innanzi a gli occhi…, ma non si può intendere se prima non s'impara a intender la lingua, e conoscer i caratteri, ne' quali è scritto. Egli è scritto in lingua matematica, e i caratteri son triangoli, cerchi, ed altre figure geometriche, senza i quali mezi è impossibile a intenderne umanamente parola; senza questi è un aggirarsi vanamente per un oscuro laberinto*. (Philosophy is written in this very large book that stays always open in front of our eyes, but that cannot be understood if we do not first learn its language. It is written in the language of mathematics, and its characters are triangles, circles, and other geometrical figures. Without these means it is impossible to understand a single word of the book, and philosophy is like wondering hopelessly in a dark maze). Galileo Galilei, Il Saggiatore, 1623. Chapter 6. By philosophy, Galileo meant what we now call science. Remarkably, Galileo was completely wrong in his thesis on the origin of comets discussed in the book, but he was extraordinarily right in his methods of reasoning, that set the foundation of science.

2 *Per lo che vo io pensando che questi sapori, odori, colori … non sieno altro che puri nomi, ma tengano solamente lor residenza nel corpo sensitivo, sì che rimosso l'animale, sieno levate ed annichilate tutte queste qualità […]. Materie sottili e tenui...che entrando per le narici, vanno a ferire in alcune mammillule che sono lo strumento dell'odorato, e quivi parimente son ricevuti i lor toccamenti e passaggi con nostro gusto o noia.* (Therefore, I am thinking that these tastes, odors, colors are nothing but sheer names, that reside only in our body. Once one removes the body, they are annihilated. These thin and delicate bodies by entering our nostrils wound some little breasts that are our instrument of olfaction, and here their touch and trail is received, giving us pleasure or pain) Galileo Galilei, *ibidem*.

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