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Taste: from peripheral receptors to perception

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Early in 2020, *Current Opinions in Physiology* approached us with the concept of publishing a special issue dedicated to the sense of taste. We assembled a collection of authors who were willing to contribute short topical essays, and written in ways that are often not possible in traditional review articles. Many of these essays include speculation, generalities and reassessment of neglected findings, others are succinct overviews of particular aspects of taste. We hope the essays in this Special Issue may inspire and suggest areas that are ripe for new experimentation to address unresolved questions.

Taste, one of the 5 primary senses, has lagged the other senses in the precise physiological elaboration of mechanisms at the molecular, cellular, and system levels. One possible explanation is a paucity of anatomical guidance. The laminar order of the retina, the elegant spiral of the cochlea, and the dimensional orientation of semi-circular canals all hint at a systematic, functional organization. In contrast, taste buds are distributed across oral epithelium and the receptor cells in each taste bud are not easily classified by shape or location. The neurons for gustation also are not organized in any obvious pattern, whether one examines peripheral sensory afferents, first and subsequent central relays, or cortical structures. Thus, without guidance from anatomy, electrophysiological patterns have been difficult to connect from one level to another. The last two decades have witnessed the field of taste research making impressive headway breaking through these barriers.

As Finger and Barlow describe in a succinct history, molecular markers for taste bud cells have been identified and, combined with confocal and electron microscopy, have finally yielded a reasonably clear picture of the many cell types in taste buds. Another interesting and unexpected complexity is the origin of the different cell types during the lifelong turnover and regeneration of taste buds (quite unlike many other sensory epithelia). Recent years have brought an understanding of the identity of progenitor cells that replenish the taste bud, and the transcriptional programs that guide cell type identity.

G protein-coupled receptors for taste (TAS1Rs,TAS2Rs) were identified over 20 years ago. New information about these receptors as essential detectors of nutrients and toxins, continues to be revealed. Risso et al. explore how different species and populations have utilized polymorphisms in the coding sequences for TAS1Rs and TASRs to evolve, adapting

to detect novel nutrients, guard against geographically-specific toxins and pathogens, and thereby conferring selective advantage for populating new niches.

TAS1Rs and TAS2Rs are also found on the surface of a surprising variety of cells throughout the body. Harmon et al. discuss how TAS2Rs, originally identified as detectors of bitter tastants, may serve also as key elements of a wide-ranging defense network throughout the body – orchestrating innate immunity responses in airways, gastrointestinal and urinary tracts, and triggering endocrine and behavioral defense responses. Continuing on the theme of the sentinel role of taste receptors, Hanselman et al. elaborate how receptors for fatty acids may guide a preference for fatty and fermented foods in addition to functioning as taste detectors for dietary fats. Separate receptors for long-chain and short-chain fatty acids appear to participate in opposing pathways for satiety and reward, beyond the simple perception and identification of fat taste.

Rhyu and Lyall review receptor binding studies that expand the range of compounds that TAS1Rs and TAS2Rs detect. They describe how a number of short peptides (2–4 amino acids) may activate taste receptors to elicit umami or “kokumi”, and modulate bitter, sweet, and salty taste responses. Thus, short peptides potentially may add complexities to sensory perceptions, as suggested by nerve recordings and behavioral studies.

Barry Green suggests an intriguing taste receptor-based mechanism for the well-documented taste illusion that warming the tongue elicits the sensation of sweet. Green posits this sensation is generated by thermally-induced conformational changes in the sweet taste receptor and subsequent activation of downstream effectors. The intensity of this illusory sweetness is modulated by intricate neural circuits in the brain.

Taste GPCRs underlie detection of sweet, bitter and umami. Sour and salty are detected by very different receptors. Liman and Kinnamon review the elegant identification of Otop1 as a proton-selective channel and a principal sour taste receptor through painstaking expression cloning and biophysical analyses. Otop1 channels in sour-sensing taste bud cells allow proton influx, thereby, depolarizing these cells. The signal is transmitted to afferent fibers that express serotonin receptors.

Over the years, a great deal of effort from many labs has been devoted to characterizing responses to salty taste stimuli. After this Special Issue was commissioned and authors had been finalized, an elegant report that elucidated the molecular basis of a major component of salty taste was published. In a *tour de force*, Akiyuki Tarano’s laboratory demonstrated that salt taste preference in rodents is mediated by ENaC channels in a subset of taste bud cells. ENaC channels allow Na^+ influx, thereby depolarizing these cells and evoking action potentials, resulting in neurotransmitter (ATP) release. Importantly, these Na-sensing taste cells lack voltage-gated Ca^{2+} channels and secrete ATP through CAHLM1/3 channels, independently of *Ca^{2+} elevation*. CAHLM1/3 channels had previously been shown to underlie non-vesicular ATP secretion in response to sweet, bitter and umami tastes. Regarding salty taste, Albertino Bigiani reviews the literature on salt detection mechanisms in rodents, and proposes that humans may not hav a comparable mechanism to recognize

Na^+. Additional receptors and transduction mechanisms for salt taste may remain to be discovered.

In addition to TAS1R-mediated sweet taste, some oral sugars are transduced through glucose transporters and ATP-sensitive K^+ channels, a mechanism "borrowed" from pancreatic beta cells. Yoshida et al. discuss how, in taste buds, glucose transmporters help to integrate sensory detection of sugars with endocrine mechanisms for energy homeostasis, particularly those involving insulin in the short term and leptin more chronically. Banik and Medler discuss how the transduction mechanisms for sweet and bitter include many variations, exceptions, and alternative pathways for receptors, downstream effectors and even the types of cells that detect these tastes. Anthony Huang reminds the reader that many pharmaceuticals, particularly those that are immunomodulatory, produce taste disturbances as side effects. Drawing on relevant pharmacological literature, he proposes mechanisms by which disrupted cellular signaling within taste buds may result in a variety of dysgeusias.

Taste buds are not just for taste any more. Mistretta and Bradley argue that fungiform papillae – the structures on the anterior tongue that house taste buds – do more than provide support and elevate the bud to capture oral tastants. These papillae may be intricate sensory end organs for temperature, touch, and chemesthesis as well as taste. The additional modalities stem from transduction events in sensory fibers of geniculate and trigeminal cranial ganglia that terminate in and around taste buds. They raise the possibility that epithelial keratinocytes participate in certain sensations. In his contribution, Christian Lemon elaborates on trigeminal transduction mechanisms for thermal stimuli. He discusses how these signals are integrated in multisensory neurons in the pons, and how this information may influence ingestion.

Stephen Roper's piece recaps how morphologically and functionally distinct cells within taste buds communicate among themselves in addition to synapsing with afferent fibers that penetrate into the bud. Cell-cell communication in taste buds is mediated by neurotransmitters that are released by vescular exocytosis or are secreted through CALHM1/3 or through electrical synapses (gap junctions). Nirupa Chaudhari describes the novel finding that most gustatory afferent fibers that innervate taste buds possess abundant $GABA_A$ receptors. Although no role for GABA has yet been demonstrated in taste buds, this contribution speculates on possible functions for GABA at central synapses, at the neuronal somata in gustatory ganglia and proposes plausible models for GABA function in trafficking and/or signaling at taste bud- afferent fiber synapses. Ohman and Krimm review recent studies showing that the peripheral axons of gustatory afferent neurons innervating taste buds vary widely in their morphology and branching patterns. The suggestion is that these structural differences underlie differences in innervation patterns, the extent of convergence of taste bud cells onto individual neurons, and eventually, differences in neural coding of taste quality and intensity.

Several contributors to this issue have critically assessed questions of coding along the gustatory axis from brainstem to cortex, including a persistent and thorny dichotomy in the field between "labelled line" (or "spatial coding") models and other more distributed "across-fiber" (or combinatorial) patterns. Patricia Di Lorenzo cogently argues that both

models may apply in the taste periphery (i.e. at the level of taste buds and afferent gustatory neurons), but neither is sufficient at higher levels in the taste axis. Instead, olfactory and somatosensory (temperature, texture) signals are integrated with taste signals to produce a sensorimotor system for ingestion. In a related contribution, but drawing on different types of data, Boughter and Fletcher posit that there is no primary sensory cortex for taste. The insula, often referred to as "gustatory cortex" is really a multimodal processing center in the brain, with reciprocal connections to the thalamus and amygdala. They propose,that the insular cortex is part of a broad circuit for feeding and foraging behavior. Lin et al. argue against the concept of cortical neurons being dedicated to specific and narrow functions or features of a sensory stimulus. Instead, the function of a cortical neuron is best understood by studying stimulus-evoked responses in the context of the activity of the neural network in which the neuron participates; timing is everything.

Brain imaging studies in human subjects are remarkably consistent with observations and interpretations derived from studies on animal models. Jason Avery uses findings from fMRI to demonstrate that there is no discrete topographical mapping of taste qualities in the human cortex: signals for very distinct qualities are fully intermingled. Recognizing and discriminating among different tastes, then, is an emergent property of a complex spatiotemporal code, perhaps not unlike that seen for olfaction. Kathrin Ohla, relying on electrophysiological observations, elaborates on the multimodal integration that is observed in the human insular cortex. The representation of gustatory sensory information is dynamic, changing in association with internal states, emotions, and motivation.

Finally, Richard Mattes challenges the common premise that the function of taste is to identify nutrients for ingestion. The inherent taste qualities (sweet, salty, sour, bitter, umami, fat) and intensities alone are unreliable determinants of food choice. Food and drink intake is guided by a combination of taste properties and learned behavior that integrates metabolic signals with various sensory characteristics.

Biography

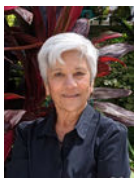

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Fig. 1.
Hermann Armin Kern: Old Man in the Kitchen (1875). Slovak National Gallery.