the phenotypes induced by loss of Aurora B activity. Hesperadin, another ATP-competitive inhibitor, inhibits both Aurora kinases but has a higher specificity for Aurora B *in vitro* and *in vivo*.

What is the relationship of Aurora kinases and cancer? All three members of the Aurora kinase family are overexpressed in multiple solid tumors, which is perhaps not surprising considering their functions in cell division. As more and more small-molecule Aurora kinase inhibitors are being developed, these inhibitors can be used not only for cell-biological studies on the functions of Aurora kinases, but also for developing new anti-cancer drugs. These inhibitors obstruct Aurora kinases, which in turn leads to aberrant mitosis. As a result, the p53-dependent checkpoint is activated and results in the induction of a G1-like cell-cycle arrest. Several small-molecule inhibitors of Aurora kinases, such as VX-680, PHA-739358 and AZD-1152, have shown anti-cancer effects in preclinical and clinical trials.

What more do we need to know? Although multiple functions and substrates of the Aurora kinases have been identified, there is still a lot of missing information. For example, the functional consequences of phosphorylation have been thoroughly investigated for only a limited number of substrates. Also, the upstream signals that guide the cellular localization and thus contribute to the functions of the Aurora kinases remain to be elucidated. Finally, how the Aurora kinase activities are differentially regulated and how their activities are integrated with other mitotic kinases are also important avenues for future studies.

Where can I find out more?

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Primer

Mammalian taste perception

Paul A.S. Breslin[1] and Alan C. Spector[2]

The sense of taste is activated when certain classes of chemicals contact specialized epithelial taste receptor cells in the tongue, palate, throat and, in some species, near the epiglottis and the upper esophagus. The various categories of taste stimuli detected at the periphery are processed alone, or in combination, to stimulate the percepts associated with nutrients and toxins, to drive complex ingestion or rejection behaviors, and to initiate physiological processes that aid in the digestion and assimilation of food.

Our objectives here are to review some basic principles of taste function and its underlying neurobiology, while highlighting some of the methodological and interpretive issues associated with the assessment of taste perception in humans and nonverbal mammals.

Taste qualities and the nutrients with which they are associated

By convention, most researchers believe that human taste perceptions can be categorized into one or more combinations of five taste qualities, each of which is associated with a particular biologically relevant class of compounds. Sweet sensations are associated with the presence of simple carbohydrates; umami taste is generated by amino acids and small peptides; salt taste is associated with the presence of sodium and sometimes other ions; sour taste is generated by acids; and bitter taste sensations arise from stimuli that are potential toxins, such as various plant alkaloids.

The extent to which stimuli that activate these taste qualities represent stimulus primaries from which most, if not all, taste sensations can be constructed, just as mixtures of short, medium and long wavelength visible light primaries can stimulate most colors in the visual spectrum, remains to be rigorously proven. Some species of mammals seem unable to experience some of these qualities, while others may perceive taste qualities in addition to these five, such as those generated by polysaccharide starches or fat stimuli. Nevertheless, converging lines of neural and psychophysical evidence support the idea that there are a small number of taste qualities.

Sweetness

Most animals actively seek and consume foods that are sweet-tasting to humans. Naturally occurring sweeteners include calorie-rich sugars such as glucose, an essential metabolic fuel for the brain. Several other natural compounds, structurally unrelated to carbohydrates, also taste sweet. Most commonly, certain amino acids, such as glycine, taste sweet to humans. The adaptive significance of an animal's ability to identify sources of calories from glucose, fructose or sucrose needs no explanation. The avidity for sweet-tasting compounds is not universal, however. Felines do not prefer sugars, having seemingly lost their ability to perceive them as a result of a mutation in the gene for a primary taste receptor that is normally activated by these compounds. This likely has little effect on a cat's reproductive fitness because it is an obligate carnivore, and generally eats a balanced diet without need to forage for specific nutrients. This provides an example of how an animal's ecological niche and evolutionary history has shaped the gustatory system in specialized ways.

Umami or savory taste

Umami taste, stimulated by amino acids or peptides, is a general indicator of protein in food. There is still debate as to whether amino acids such as glutamate represent a primary taste stimulus, or whether umami taste may be derivative of the other taste sensations. Umami is a 'helper' quality that triggers a strong response in humans only in the context of other flavors. This may be due to the fact that free amino acids rarely appear alone in nature. In appropriate contexts, however, such as in meats and other savory foods, amino acids such as glutamate are highly desirable to us. While rats and mice will readily ingest amino acids, it is not clear that they perceive a distinct umami taste quality. Glutamate appears to share perceptual attributes with sucrose in these rodents, which contrasts with the human perception of glutamate, which is rarely, if ever, described as sweet.

Salty taste
Salty taste is stimulated by a variety of salts in humans, with the most effective stimulus of this sensation being NaCl. Anions influence the salty quality of sodium salts and, in humans, may add sourness, bitterness or even sweetness. In humans, many non-sodium salts, such as KCl, also have a salty characteristic in addition to other qualitative attributes. In rodents, however, the qualitative taste sensation that one could call saltiness comes specifically from the sodium (or lithium) cation. In herbivores and some omnivores, there is a high premium for finding sodium in the environment because of the inability to store enough of this required electrolyte in the body. Given that sodium is essential for life, no other ion can replace it, and animals are constantly losing it in various excretory and secretory processes, the adaptive significance of the presence of a specific sodium taste detector in these animals is clear.

Sour taste
Sour taste, which is stimulated by acids, is not associated with a specific group of nutrients. Yet it is still highly desirable in foods, and acidic additives are often used by humans to make foods sour. Sour taste appears to be due to protons, and unlike salt taste in humans, anions do not appear to significantly alter the sour taste quality, only its intensity. That is, strong acids, such as HCl are less effective sour stimuli than weak organic acids such as citric at a similar pH, but both are purely sour tasting for humans. Sourness may have co-evolved with sweetness as an indicator of when fruits should be consumed. Acidity, and thus sourness, is also an indication of fermentation, which can enhance the bioavailability of nutrients in certain foods. But strong sourness is typically avoided, which may protect against consumption of acids at concentrations that can damage tissues and teeth.

Bitter taste
Bitter taste, and its unpleasantness at high intensities, appears to be a warning system to protect us from ingesting toxins. Toxins are present to some degree in virtually every plant. Indeed, most plants, even some nutritious cultivars such as olives, in their unprocessed state taste bitter. Among humans, bitter taste is highly variable and randomly sampled individuals will perceive a single stimulus as ranging from not bitter at all to extremely bitter. Genetic polymorphisms in bitter taste receptors are likely the result of the taste system rapidly evolving in response to changes in dietary ecology and migrations of animals over long periods of time. Similar genetic variations in bitter taste sensitivity are also seen among strains of mice.

Other taste qualities
In addition to the basic qualities of taste described, there are several other taste qualities that may not be less important but are less understood. Rodents, at least, may have a polysaccharide or *starch taste* that is distinct from simple sugar taste. The existence of a *fat taste* is hotly debated, but is logical given that the taste system detects other macronutrients. Animals clearly sense fats in the mouth, but it is unclear whether this is based on tactile and olfactory signals alone or in combination with fat taste. *Metallic taste* has been described for centuries, but this distinct sensation may be a combination of several taste qualities with somatosensory inputs from ion-induced currents in the tongue. There have also been old and new references to an *astringency taste*. Astringency, however, can comparably arise from stimulation of both gustatory and nongustatory epithelia, suggesting it is a sensation independent of taste.

The biology of taste perception
The organization of sapid compounds into perceptual classes by quality can first be observed at the interface between the nervous system and the environment — the taste receptor cells. The way chemical activation of taste receptors stimulates taste bud cells and ultimately the neuronal fibers connected to them, and, in turn, the way these inputs are channeled through the brain, represents the neurobiological substrates of the perceptual and behavioral taste functions described here. It is thus worthwhile to describe the basic features of these substrates.

Taste-sensitive epithelia, and gustatory nerves
Taste receptor cells are arranged in rosette-shaped groups of 50–100 called taste buds. In many mammals, including rodents and humans, taste buds are distributed in distinct fields throughout the oral cavity, with each field innervated by a different branch of either the 7th, 9th, or 10th cranial nerve (CN VII, IX and X, respectively; Figure 1). Human and rodent taste buds on the anterior tongue are found in specialized epithelial protrusions called fungiform papillae. The taste bud cells in this region of the tongue are innervated by the chorda tympani nerve (a branch of CN VII). The lingual branch of the trigeminal nerve (CN V) also supplies the fungiform papillae and its fibers surround taste buds, providing some of the initial neural infrastructure for the substantial interaction between the oral somatosensory (tactile, thermal and pain-sensing) and gustatory systems. A branch of CN VII, the greater superficial petrosal nerve, also innvervates large numbers of taste buds on the palate. Taste buds in the posterior tongue are found in the foliate papillae (a row of slits on the posterior lateral margins) and the circumvallate papillae (circular trenches on the posterior dorsal surface). Taste buds lie within walls of the trenches and are innervated by the lingual tonsilar branch of the glossopharyngeal nerve (CN IX). Taste buds also occur in the laryngeal epithelium of some species where they are innervated by the superior laryngeal branch of the vagus nerve (CN X). Their location and their chemical response profile suggest a role in protecting the airways.

One interesting property about taste bud cells is that they are constantly undergoing apoptosis and regeneration. The average lifespan of a taste bud cell has been estimated to be about 10 days. This turnover and the presence of morphologically normal taste buds depend heavily on the presence of intact innervation. When a gustatory nerve is transected the taste buds it supplies degenerate (although in some species some taste buds remain). Gustatory nerves therefore have a trophic influence on the morphological and functional integrity of taste buds. Gustatory nerves also have a noteworthy proclivity to regenerate after transection and to find their way back to their native receptor fields, where they induce taste bud reformation, demonstrating tropic guidance between axon and receptor cell. When the nerves regenerate, taste function, for the most part, returns to normal. In light of the impressive degree of plasticity in the tissue responsible for the initial stages of stimulus encoding, it is remarkable that our perceptual taste world is relatively stable. Accordingly,

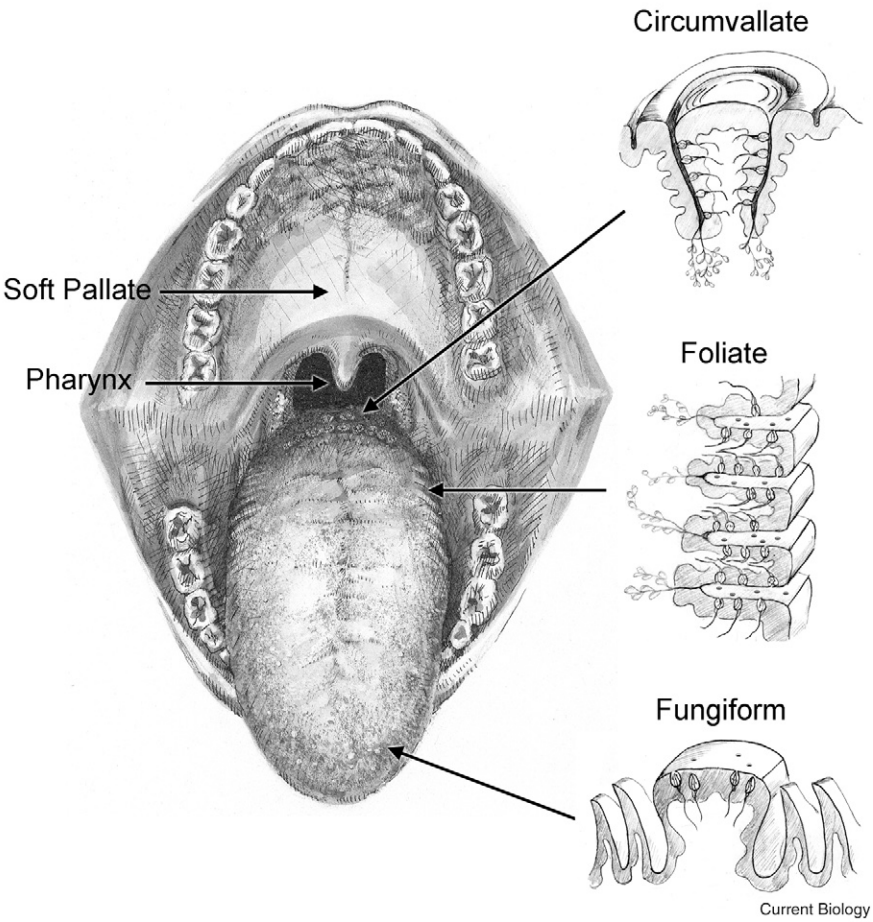

Figure 1. The taste receptor fields of the human oral cavity.

This diagram shows the human taste receptor fields by depicting the hyper-extension of the mouth. The anterior tongue contains taste buds within fungiform (mushroom-shaped) papillae innervated by the chorda tympani branch of cranial nerve VII (Facial). Posterior tongue contains taste buds within the trenches of foliate (leafy) and circumvallate (walled tower-shaped) papillae innervated by the lingual-tonsilar branch of CN IX (Glossopharyngeal). The glands appearing below foliate and vallate papillae (insets) are Von Ebner's glands that secrete into the folds of the papillae. Soft palate contains taste buds on the surface of the epithelial sheet without papillary structures innervated by the greater superficial petrosal branch of the CN VII. The taste buds posterior to the pharynx are innervated by the superior laryngeal branch of CN X (Vagus). Insets depict enlarged views of taste buds within papillae. Artwork by Robin Rice; insets by Karen Yee.

there must be some mechanism that allows peripheral gustatory nerve fibers to match with their appropriate receptor cell. The gustatory system clearly offers opportunities to learn more about mechanisms of neural plasticity.

Taste receptors

Several types of taste receptor cell (e.g. Type I–IV) have been identified in taste buds based on their morphology, cytoplasmic electron density, and cytohistochemical profiles. The actual receptor proteins are found in the apical membranes of a subset of the taste bud cells. The apical membranes protrude through a break, called the taste pore, in the stratified squamous epithelium lining the oral cavity. This lining as well as the tight junctions between taste bud cells provides protection from the potentially harmful chemicals placed in the mouth. Bitter, sweet and umami tasting stimuli bind to seven-transmembrane spanning G-protein coupled receptors, whereas salty and sour stimuli are thought to interact directly with ion channels. Interestingly, many of the taste G-coupled receptors and their critical intermediary transduction components are found primarily in Type II cells, which do not have conventional synapses with gustatory neural fibers. The neural synapses occur primarily with Type III cells. Such findings lend support to the view of the taste bud as a processing unit.

Amino acids, sugars, artificial sweeteners and some sweet tasting proteins are recognized by heteromers of the T1R family of receptor proteins: T1R1, T1R2 and T1R3. The T1R1 + T1R3 heteromer binds L-amino acids, and its activation is facilitated by the presence of 5′ ribonucleotides such as inosine monophosphate. In humans, the T1R1 + T1R3 receptor seems to recognize only L-glutamate and L-aspartate. Several other amino acid receptors, for example, the splice variant of the metabotropic glutamate receptor subtype 4 (mGluR4), have also been suggested to be receptors of umami ligands. The sensation of sweetness appears to arise in large part from activation of the T1R2 + T1R3 heteromer. In the case of both L-amino acid and sweetener receptors, gene knockout data from mice have convincingly demonstrated the necessity of the T1R heteromeric receptors for normal taste perception, although each protein may be capable of forming low affinity homomeric receptors. Whether the T1R receptors alone are *sufficient* for amino acid and sugar taste perception has been more difficult to determine.

Bitter stimuli are ubiquitous in the plant and animal world and consequently act upon the largest set of oral taste receptors. At last count, humans have 25 putatively functional bitter receptor genes coding for G-coupled receptors, referred to collectively as the T2R family. The T2Rs vary significantly in their binding profiles, some appearing specific for only a few compounds, while others are activated by whole chemical classes. At present, more than half of these receptors remain orphans with respect to their ligand binding characteristics. A couple of interesting features of T2R expression have implications for taste coding. First, many T2Rs are co-expressed on subsets of taste bud cells, at least in rodents, suggesting that these animals should have difficulty discriminating many T2R ligands. Indeed some behavioral data support this prediction. Second, taste bud cells that express T1Rs rarely, if ever, express T2Rs. Thus, the receptor cells signaling the presence of sweet-tasting ligands and those signaling the presence of bitter-tasting ligands are segregated at the very beginning of processing even

with a single taste bud. Interestingly, studies of the response properties of individual taste bud cells contrast with the molecular expression and behavioral data just mentioned. Some taste receptor cells appear to respond selectively to various bitter tasting ligands, while others appear to respond to both quinine and sucrose. The apparent contradictions between the receptor expression data and the response properties of taste bud cells remain to be fully resolved, but likely involve the taste bud as a multicellular signal processing organ as suggested by recent reports. It is also worth noting that T1R and T2Rs have been found to be expressed in the gastrointestinal tract, where they may play a role in enteric nutrient signaling.

Salt taste in rodents is mediated by at least three ion channels. The first is an amiloride-sensitive ion channel that is thought be an epithelial sodium channel (ENaC). In rodents, this channel is very selective for Na^+ (and Li^+), giving rodents an impressive ability to detect and recognize sodium salts regardless of the anion. A variant of the Transient Receptor Potential V1 (TRPV1) channel has been implicated as a nonselective cation channel involved with responses to a variety of salts. However, TRPV1 knockout mice have behaviorally normal NaCl detection thresholds and are no more disrupted by amiloride-mediated ENaC blockade than are wild-type mice, suggesting that NaCl detection can occur through other transduction pathways in addition to those based on the ENaC and TRPV1 channels. In humans, amiloride does not appear to alter the saltiness of NaCl, but does reduce its very weak sour side-taste. This suggests species differences in the specific roles that these ion channels play in signaling salt taste.

The receptors mediating sour taste have also remained elusive for many years, with several ion channels considered as candidates, including isoforms of the acid sensing ion channel (ASIC), hyper-polarizing-activated cyclic nucleotide-gated (HCN) channels, two-pore domain potassium channels (K2P), and others. Recently, a member of the PKD1 family of TRP channels, the polycystic kidney disease-like ion channel PKD2L1, which is expressed in the apical region of a subset of taste bud cells, has been implicated as a component in taste transduction involving acid stimuli. The chorda tympani nerve in mice that had taste bud cells that express PKD2L1 specifically ablated via forced co-expression of pertussis toxin, was completely unresponsive to a variety of acid stimuli, but displayed normal responses to several sweeteners, amino acids, bitter-tasting ligands, and NaCl. Interestingly, cells that express PKD2L1 do not express T1Rs or T2Rs, further supporting the view that the receptors mediating various taste qualities are distributed in a segregated fashion among taste bud cells. While the cellular-knockout data indicate that receptor cells expressing PKD2L1 are necessary for sour taste, it does not explicitly prove that PKD2L1 is the actual molecular receptor.

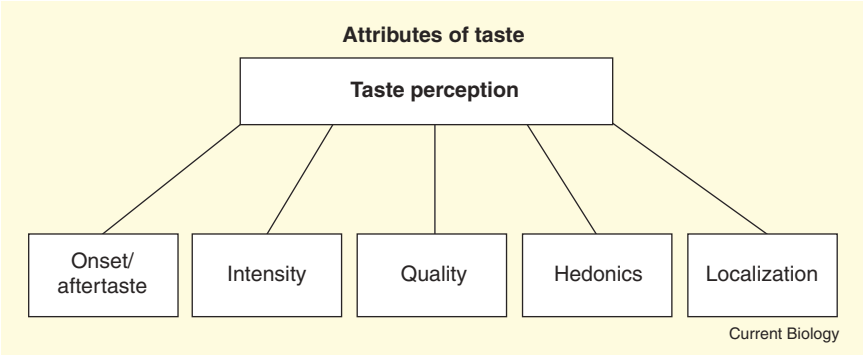

Figure 2. The psychological attributes of a taste percept.
The percept of taste from any given stimulus or solution is principally thought to consist of qualitative experiences labeled salty, sweet, bitter, sour and umami. Most taste percepts will also be composed of distinct additional attributes: intensity, hedonic, oral localization, and temporal features (rise and decay and aftertaste).

Sensory discriminative function

As discussed above, taste stimuli can be categorized by the qualitative sensations they evoke. Adjectives such as sweet, sour, salty, bitter and umami are unique descriptors used by humans, but the way that many mammals categorize taste compounds suggests that they experience similar classes of qualitative taste perceptions (Figure 2). Importantly, the perceived quality of taste is dissociable from its hedonic properties to a large degree. This raises the question: what adaptive function does a taste quality serve? One possible answer is that it allows animals to identify chemical stimuli that serve as cues for the consequences of ingestion. Thus, the identification of taste stimuli by their perceived quality allows an animal´s choices among various nutrients and toxins to be molded by experience.

Neural coding of taste quality and intensity

Understanding how the nervous system represents information about the qualitative features of a taste is challenging, in part because taste quality does not obviously co-vary along a physical dimension of chemical stimuli in the way that hue, for example, varies with the wavelength of light. It is generally accepted, however, that taste intensity is represented by a neural firing rate code. The higher the concentration, the greater is the rate of activity in taste-responsive neurons.

With respect to taste quality, most investigators have favored a spatial coding model in which the quality of a taste stimulus is represented by the identities of the neurons that are active, as opposed to the pattern of activity over time within a neuron; the latter being a temporal code. The two spatial coding models that have been proposed are the labeled-line theory and the across-neuron pattern theory. In the labeled-line view, activity in a dedicated subset of neurons leads to the generation of a specific taste quality. In the across-neuron pattern view, taste quality is represented by the pattern of activity across a large ensemble of neurons. The labeled-line model is in one sense subsumed by the across-neuron pattern model. However, the former coding theory specifies a critical characteristic that distinguishes it from the latter: namely, in the labeled line model, activity in a specific subset of neurons is both *necessary* and *sufficient* to generate a specific qualitative taste (Figure 3).

The arguments used to support either model are mostly based on correlational

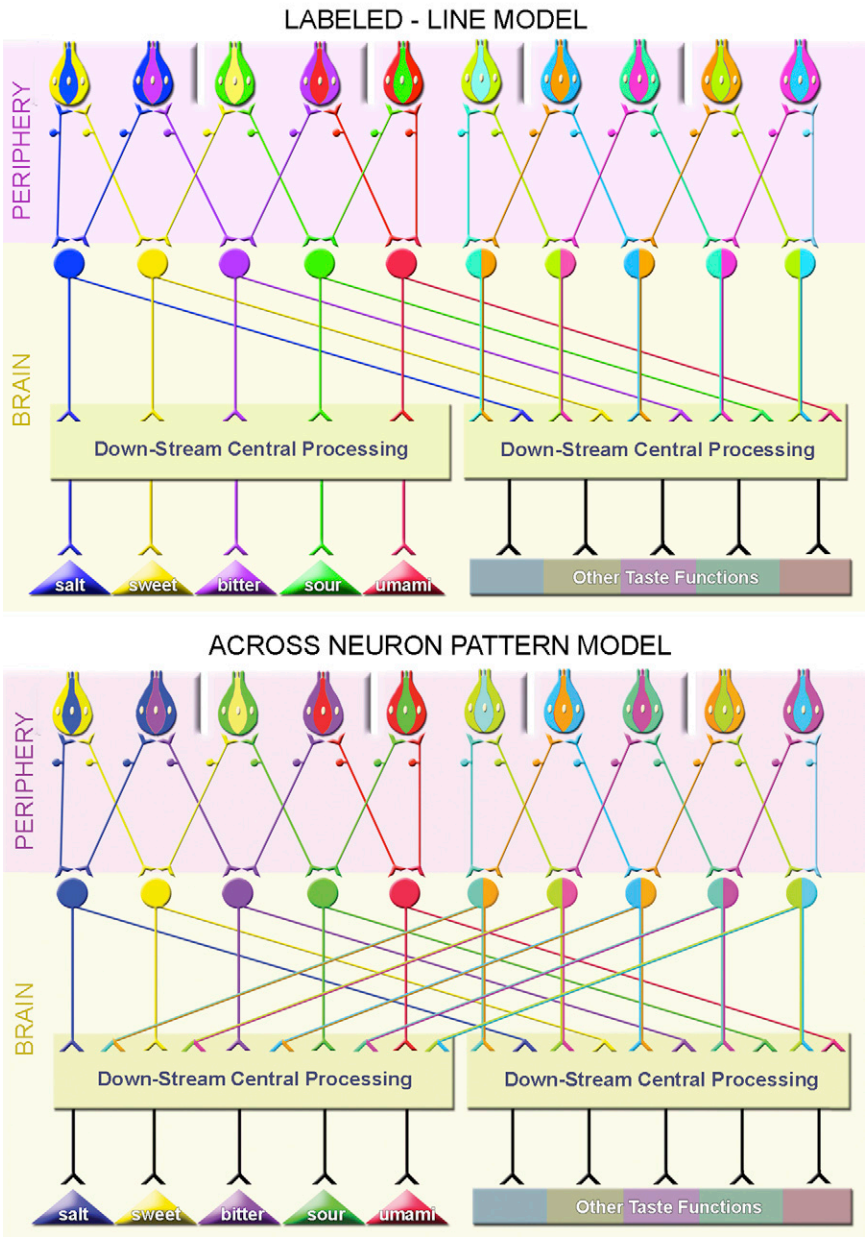

Figure 3. Idealized models of labeled-line versus across-neuron pattern coding of taste quality.

The top panel depicts labeled-line coding of quality and the bottom panel depicts across-neuron pattern coding. In the idealized version of labeled-line coding, activity in a dedicated subset of relatively narrowly tuned neurons gives rise to a specific taste quality perception (left side of panel). Activity in these neurons is necessary and sufficient for the specific quality perception to occur. Thus, the elimination of such a neuronal subset should affect the perception of its associated taste quality without affecting the others. Importantly, this model of quality coding does not preclude the existence of broadly tuned taste neurons (right side of panel). In the idealized version of across-neuron pattern of quality coding patterns of activity in large ensembles of both narrowly and broadly tuned neurons lead to the perception of specific taste qualities (left and right side of panel). Different patterns lead to different qualitative perceptions. Various incarnations and subcomponents of these models have appeared in the literature. Whether the specific features of these models hold true for all or any mammalian species is hotly debated.

observations or are indirect. In one study, mice were engineered to express a modified κ-opioid receptor in taste bud cells. When receptor expression was targeted to T1R2-expressing taste cells, the mice showed intake preferences for an opioid agonist to which wild-type mice were indifferent. When the receptor was targeted to T2R-expressing taste cells, mice avoided the agonist. While these results implicate a spatial code, they do not necessarily rule out a temporal coding component, nor do they distinguish between the two categories of spatial codes.

There are classes of fibers in the gustatory nerves that are relatively narrowly tuned to respond to compounds that generate a single perceptual taste quality. Despite this narrow tuning peripherally, convergence is evident as soon as these signals reach the brain, and taste-responsive neurons in gustatory structures are a more heterogeneous population from the standpoint of tuning. Many of these neurons are broadly tuned, responding to compounds from more than one perceptual class, for example, sweeteners or NaCl. However, some remain narrowly tuned. Because it is unclear to which functions a given taste-responsive neuron contributes, it is difficult to use the presence of broadly and narrowly tuned units as evidence for one coding model over another. Ultimately, until select classes of taste-responsive neurons can be silenced and the consequences on taste quality identification assessed, it will not be possible to definitively test the relative merits of the labeled line and across neuron pattern theories. It should also be mentioned that although the above discussion has focused on spatial coding models, it is premature to completely rule out the possibility that information on taste quality can be represented by some temporal feature of the neural activity as suggested by some investigators.

The multimodal highly integrative nature of taste

In addition to chemical inputs, taste perception and resulting behavioral responses also rely on thermal and tactile inputs. Taste-responsive neurons throughout the central gustatory system often intermingle with or are nearby oral somatosensory neurons, and some respond to mechanical and thermal stimulation. Furthermore, central projections from visceral receptors roughly parallel gustatory projections throughout the brain, consistent with the close functional relationship between taste and other senses affecting feeding behavior. In fact, some taste receptors, such as T1Rs and T2Rs, are expressed in the gut, though their function remains to be fully

explained. Taste-related areas of cortex also show responsiveness to odors, oral temperature, touch, pain, visual and auditory input. Thus, the convergence of sensory inputs in some cortical areas provides the anatomical infrastructure for integration that might subserve the perception of flavor. Recent functional magnetic resonance imaging (fMRI) reveals gustatory stimulation in humans also regularly activates other regions of brain as well, such as those implicated in processing related to emotion, attention, planning, reward and feeding.

Individual differences in taste quality perception

Individual differences in ability to taste are ubiquitous among humans, with variation in bitterness perception most common. Environmental factors might account for some differences, but many are genetic. Genes for sugar and amino acid receptors (T1Rs) and those for bitter-ligand receptors (T2Rs) are highly polymorphic among human populations, and changes in those genes can render receptors ineffective. Differences in sour taste are known to be heritable, but their underlying cause is not yet clear.

Sensitivity to the bitter compound phenylthiocarbamide (PTC), detected principally by T2R38, is the most well studied difference. The gene for this receptor is polymorphic, but two haplotypes account for the majority of the alleles globally: the first, labeled PAV — named for the amino acid identities at specific polymorphic positions in the protein — codes for a receptor sensitive to PTC; the second, labeled AVI, codes for an insensitive receptor. Perceptual differences are strong enough to enable some people to taste vegetables such as broccoli or turnips as less bitter than perceived by their heterozygous and homozygous PAV counterparts, because these vegetables contain glucosinolates, which are structurally similar to PTC and are likely the natural ligands for this receptor.

Psychophysical assessment of discriminative taste characteristics in humans

Sensitivity

Human taste studies have principally investigated sensitivity to, and perceived intensity of, individual taste solutions. Two main types of sensitivity have been studied: first, absolute sensitivity or detection thresholds of stimulus concentrations dissolved in water; and second, differential thresholds or just-noticeable-differences that measure the minimal detectable change in intensity. Threshold sensitivity generally varies with the class of compound. For example, rodents and humans detect most toxins in the micromolar range or lower and detect sugars in the millimolar range. Thus, the gustatory system seems to be tuned to operate in a dynamic range that would be most adaptive, responding to potentially harmful stimuli at very low levels and responding to sugars once they could potentially provide significant calories. Similar to other sensory systems, the just-noticeable-differences (j.n.d.) for the taste stimuli that have been studied seem fixed relative to overall intensity level, as the Weber's Fraction — the ratio of the j.n.d. threshold (ΔI) to background concentration (I) — remains constant over broad ranges of I.

Intensity and quality

Intensity measures are typically used to determine the psychophysical concentration–intensity function, and can assess the maximum behavioral response of a system (the asymptote), as well as the slope of the function, which is indirectly related to j.n.d. sensitivity. Intensity functions are frequently established by measuring ratings, magnitude estimations, rankings or intensity matches to establish a baseline against which one may determine whether suppression, inhibition, or synergy are occurring with chemical admixtures. The slopes of most psychophysical intensity functions vary not only with the quality of taste, but also with the structure of the compound employed. Moreover, even a single compound will demonstrate different intensity-function slopes depending on whether it is stimulating the front or the back of the tongue.

Subjects may also be asked to discriminate stimuli that differ in structure to establish the coding dimensionality of taste. For example, failure to discriminate two stimuli that differ chemically is the basis of establishing metamers, groups of physically distinct stimuli that are perceptually indiscriminable. Such experiments are very powerful because the existence of a metameric pair suggests that the compounds generate an identical neural response somewhere in the gustatory system providing a strategy to search for neuronal circuits that might be involved in quality coding.

Mixture interactions among taste stimuli

Masking studies measure sensitivity to a stimulus against a background stimulus, such as detecting the presence of citric acid against a background of NaCl. These conditions more closely resemble those under which the taste system evolved, since we almost always experience chemical mixtures in items we eat. They also more readily reveal deficits associated with disease or age than do single stimulus studies. For example, while whole mouth detection thresholds for NaCl in water vary only slightly between young and elderly subjects, their abilities to detect NaCl in complex chemical solutions such as soup are quite different. Suprathreshold stimuli also usually affect each other when mixed, although not always reciprocally. These common mixture interactions vary depending on the compounds involved. They can be suppressive, inhibitory, and positively synergistic.

Adaptation

Taste intensity diminishes with continuous or repeated stimulation, a mechanism that maintains sensitivity to changes in the environment. The taste-specificity of the adapted response enables fine-tuning of different coding channel sensitivities during prolonged stimulation. When subjects are adapted to the bitter taste of quinine, for example, their ability to taste sweetness from sucrose is almost unaffected. This may be useful, in the context of complex taste stimulation from natural taste stimuli, and may help animals differentiate parts of plants that vary in their nutrient or toxin content.

Spatial and temporal properties of taste

Taste sensations are also spatially localizable and temporally distinguishable. For example, some bitter tasting compounds are bitter on all oral taste receptor fields, while others are bitter only in posterior tongue and pharynx. Some bitter tasting compounds elicit short-lived sensations, while others have a prolonged aftertaste. Many high potency sweeteners are easily distinguished this way from sucrose, as they differ in their temporal profile and may also differ in the perceived

location of stimulation. Such subtle attributes are generally difficult to study in nonhumans.

Psychophysical assessment of discriminative taste characteristics in other animals

Conceptual ramifications of behavioral methodology

Taste perception can never be measured directly (even in humans), and must be inferred from behavior. The most common procedure used to assess taste function in nonhuman mammals is the two bottle preference test. In this procedure, one bottle of a taste solution and one bottle of water (or a different taste solution) are placed on an animal's cage and the relative intake of the two solutions is measured. This method has the merit of simplicity, but it is interpretively limited because there are several factors other than taste, such as postingestive events, that can influence preference and intake.

Detection and intensity

Detection thresholds and intensity difference thresholds can be measured in a more purely psychophysical fashion using conditioning procedures. For example, after training an animal to respond to a taste stimulus, the concentration can be decreased until the animal no longer differentiates it from water. Animals can also be trained to respond via licks or lever presses to a standard concentration relative to higher or lower comparison concentrations, and difference thresholds can be derived that indicate the animal's sensitivity to change. These so-called animal psychophysical procedures have proven extremely powerful at discerning the effects of neural, pharmacological, and genetic manipulations of the gustatory system.

Quality

Conditioning procedures have also been used to assess perceptual differences and similarities among taste compounds in animal models. Typically, an animal is trained to perform one response (for example, press left lever) after sampling a specific taste stimulus (such as NaCl) and to perform a different response (for example, press right lever) after sampling a second taste stimulus (such as KCl). Correct responses are rewarded. Concentration of both compounds is varied so that the animals do not learn a strong vs. weak discrimination. If the animal is able to learn the task, then one can conclude that the two compounds are discriminable. Various test stimuli (e.g., NH_4Cl) can also be delivered on some of the trials to determine whether the animals will generalize their responses to one of the training stimuli more than the other providing a way to measure their perceptual similarities.

In a variation of this procedure, a conditioned taste aversion can be established to a given taste stimulus by pairing its ingestion with experimentally induced nausea and then the degree to which the animal subsequently avoids compounds that are thought to be representatives of the four basic tastes (for example, sucrose, NaCl, quinine, and HCl) is taken to reflect the relative sweetness, saltiness, bitterness, and sourness of the conditioned taste stimulus. All of these techniques provide a way for investigators to characterize taste stimuli into perceptual categories (regardless of the names used) relevant to their animal model and as such provide a functional context for neural analyses.

Affective processing of taste

The affective or hedonic component of a taste refers to whether the stimulus is liked or disliked. In more operational terms, it refers to whether the stimulus is accepted and ingested or whether it is rejected. Without question, the hedonic domain of taste function can be characterized by its fundamental role in food selection and the control of intake in both humans and animals.

Behavioral assessment of affective responses to taste stimuli in humans

Most frequently human subjects are simply asked to rate how much they like or dislike a stimulus on either a unipolar or a bipolar scale. Alternatively, subjects may be asked to rate how pleasant stimuli are or how much they want them. These measures do not all relate to each other linearly and appear to reflect different cognitive processes. Direct consummatory behavior, such as ingestion of stimuli, or appetitive behavior, such as taking stimuli home or purchasing behavior, may differ from the aforementioned rating methods even further. In short, the relative palatability of a taste stimulus depends heavily on the way it is measured, and verbal report may not always predict other behavioral actions to the stimulus, such as ingestion.

Behavioral assessment of affective responses to taste stimuli in other animals

A popular procedure for assessing the hedonic features of a taste stimulus is the brief-access test, in which an animal (usually a rodent) is presented with a taste solution for only a short time (several seconds), and the number of licks produced by the animal is measured. This technique has been used to derive orderly concentration-response functions. Another technique that has been used to measure the affective potency of a taste compound is the progressive ratio procedure in which animals are required to generate a progressively greater number of responses (for example, lever presses) in order to receive a small volume of a taste stimulus (a reward). Once the requirement reaches a certain number, referred to as the breakpoint, the animal ceases to respond. Thus, this technique measures how hard an animal is willing to work to receive a given taste stimulus.

Interestingly, when small volumes of highly preferred stimuli are infused through a chronically implanted cannula into the oral cavity of rodents, animals will respond with a set of reflex-like stereotypical oromotor responses such as tongue protrusions and mouth movements. Aversive compounds, such as quinine, elicit a different class of responses such as gaping and chin rubbing. If an aversion is conditioned to a normally palatable stimulus (such as sucrose) animals will display aversive rather than ingestive oromotor responses to the intraoral delivery of the stimulus, showing how even reflex-like consummatory responses can be modified by prior experience.

Taste-elicited physiological reflexes

Before nutrients are absorbed, sensory stimulation activates secretions governed by the parasympathetic nervous system that facilitate digestion and metabolism. Taste input appears to contribute to the afferent limb of such reflexes. The most common taste-elicited physiological reflex is salivation in response to acidic stimuli (such as lemon), but there are others as well, including a pre-absorptive release of insulin from the pancreas in response to oral stimulation with sugars. Collectively, these physiological reflexes help prepare the animal for the optimal digestion and assimilation of nutrients. Indeed, patients who lack

some of these reflexes, in particular pre-absorptive insulin release, due to disease or loss of vagal innervation from surgery, have difficulty processing foods and maintaining normal blood levels of nutrients.

Concluding remarks

Before swallowing, everything a mammal samples orally will undergo a chemical analysis provided in large part by the gustatory system. What an animal ingests both in the short-term and over a lifetime has undeniable consequences on survival. So critical are taste sensations to the recognition and enjoyment of foods, and the appropriate digestion and utilization of nutrients, that humans who acutely lose their sense of taste, such as following radiotherapy, for example, often will not eat. Thus, while we may tend to take the sense of taste for granted relative to our other sensory modalities, its significance for health and quality of life should not be trivialized.

> "*What is it like to lose your sense of taste? To know that the most luscious fruit is a cinder, and its juice flavored with copper and bicarbonate, or that a Whitstable oyster is no more appetizing than a slug? If, by a might of effort, these 'cinders' are forced down with copius fluid, the consequences are acute indigestion and vomiting. The patient is not hungry anyway, and it is easier to starve.*"
>
> E.M. MacCarthy-Leventhal, The Lancet (1959), 1138-1139.

Further reading

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Use of stable isotopes to examine how dietary restriction extends *Drosophila* lifespan

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The ability of dietary restriction to increase animal life span is often thought to arise from differential allocation of resources between somatic investment and reproduction [1–4]. In this theory, reproduction is repressed upon dietary restriction to make scarce nutrients available to somatic functions that increase survival. Here, we label nitrogen and carbon in the dietary yeast of *Drosophila melanogaster* with stable isotopes to determine whether resources are invested to somatic tissues at the expense of reproduction. We find that females on a full diet acquire and allocate more dietary carbon, nitrogen and essential amino acids (EAA) to eggs than females on a restricted diet. Full-diet females also invest more carbon, nitrogen and EAA into somatic tissue than those on a restricted diet. Thus, the longer lifespan of flies on a restricted diet relative to those on a full diet cannot be explained by greater absolute somatic investment, and high somatic investment does not ensure longevity. We find, however, that resource allocation to somatic tissue relative to investment to eggs is greatest in females on a restricted diet. To account for these patterns we propose that dietary restriction in *Drosophila* may extend lifespan through somatic investment relative to damage incurred from reproduction [5].

We labeled yeast acquired during larval and adult feeding with ^{13}C and ^{15}N and traced their allocation into eggs and somatic tissue when adults were maintained on restricted and full diets (4% and 16% yeast, respectively; see Supplemental Data published with this article online for methodological details). Survival was greater for females on a restricted diet, whereas females on a full diet presented 11-fold higher total fecundity (Figure S1 in Supplemental Data). To quantify the investment of resources into eggs, we estimated the proportional contribution of carbon, nitrogen, and EAA acquired from yeast (Figure S2 and S3) and multiplied this by daily fecundity, egg mass and egg composition. Females on both diets invested few larval-acquired resources to eggs. From adult-acquired nutrients,

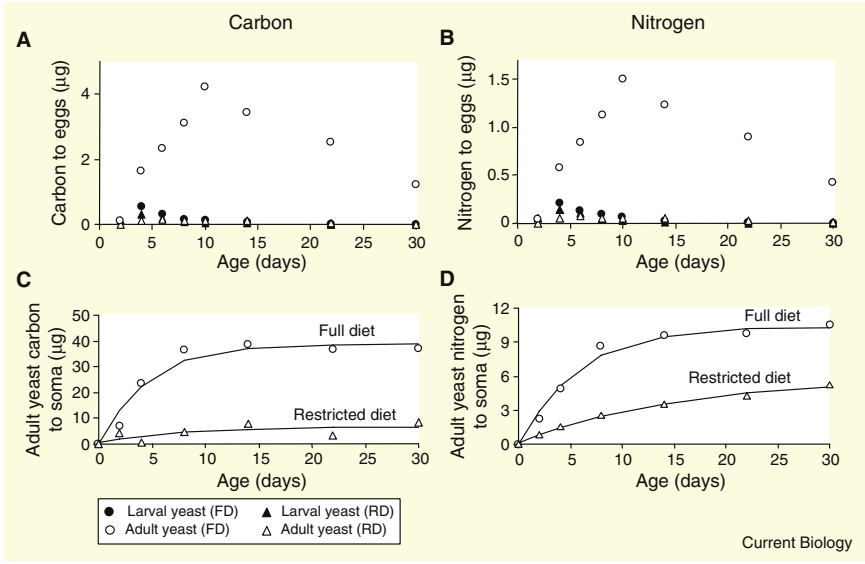

Figure 1. Daily per capita mass of carbon and nitrogen acquired from larval and adult dietary yeast, under restricted and full diets, invested in eggs (A,B), and as current content in somatic tissue (C,D).