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The Bad Taste of Medicines: Overview of Basic Research on Bitter Taste

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Abstract

Background—Many active pharmaceutical ingredients taste bitter and thus are aversive to children, as well as many adults. Encapsulation of the medicine in pill or tablet form, an effective method for adults to avoid the unpleasant taste, is problematic for children. Many children cannot or will not swallow solid dosage forms.

Objective—This review highlights basic principles of gustatory function, with a special focus on the science of bitter taste, derived from studies of animal models and human psychophysics. We focus on the set of genes that encode the proteins that function as bitter receptors, as well as the cascade of events that lead to multidimensional aspects of taste function, highlighting the role that animal models played in these discoveries. We also summarize psychophysical approaches to studying bitter taste in adult and pediatric populations, highlighting evidence of the similarities and differences in bitter taste perception and acceptance between adults and children and drawing on useful strategies from animal models.

Results—Medicine often tastes bitter, and because children are more bitter sensitive than are adults, this creates problems with compliance. Bitter arises from stimulating receptors in taste receptor cells, with signals processed in the taste bud and relayed to the brain. However, there are many gaps in our understanding of how best to measure bitterness and how to ameliorate it, including whether it is more efficiently addressed at the level of receptor and sensory signaling, at the level of central processing, or by masking techniques. All methods of measuring responsiveness to bitter ligands—in animal models, through human psychophysics, or with "electronic tongues"—have limitations.

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DEDICATION

We dedicate this review article to the memory of Dr. Barry Davis, past director of the taste and smell program within the National Institute on Deafness and Other Communication Disorders, and a friend and mentor.

Conclusions—Better-tasting medications may enhance pediatric adherence to drug therapy. Sugars, acids, salt, and other substances reduce perceived bitterness of several pharmaceuticals, and although pleasant flavorings may help children consume some medicines, they often are not effective in suppressing bitter tastes. Further development of psychophysical tools for children will help us better understand their sensory worlds. Multiple testing strategies will help us refine methods to assess acceptance and compliance/adherence by various pediatric populations. Research involving animal models, in which the gustatory system can be more invasively manipulated, can elucidate mechanisms, ultimately providing potential targets. These approaches, combined with new technologies and guided by findings from clinical studies, will potentially lead to effective ways to enhance drug acceptance and compliance in pediatric populations.

Keywords

bitter taste; flavor; children; medicines; animal models; receptors; psychophysics; genetics; palatability

1. Introduction

Most children at some point in their lives are prescribed medicine. Some refuse to take it, and they and their parents suffer the consequences. Although children are subject to many of the same ailments and diseases as adults and are treated with the same drugs, most drugs (nearly 75%) available in the United States lack Food and Drug Administration (FDA)-approved pediatric formulations and therefore do not have labeling information about pediatric safety and efficacy.[1] The lack of “child-friendly” formulations leaves an estimated 40% of the world’s children at increased risk for avoidable adverse events, such as suboptimal dosing, lack of adherence to medication regimens, and reduced access to new medicines.[2] Although recent legislation in the United States and European Union has created incentives for testing drugs in this special population,[3] this process is confounded by the requirement that the formulation be suitable for the pediatric patient population—actually a continuum of many smaller populations, such as preterm infants, term infants, infants and toddlers, preschoolers, school-age children, and adolescents.[2]

2 The Problem: A Matter of Taste

A central challenge of administering medicine to children is a “matter of taste”—drugs, by their very nature, often taste unpleasant, with bitter taste a primary culprit. More than 90% of pediatricians reported that a drug’s taste and palatability were the biggest barriers to completing treatment.[2]

Most drugs work by interfering with physiological processes within cells, so medicines have the potential to be toxic when ingested in sufficient quantity. Bitter taste is thought to have evolved as a deterrent against ingesting toxic substances,[4] which may explain why many drugs taste bitter. The basic biology of the child, as reviewed here, explains why children (and adults) reject bitter-tasting drugs. In fact, bitter compounds are effective agents in deterring pediatric poisonings when used in conjunction with other preventive measures, such as child-resistant closures.[5]

Although many solid oral dosage forms (e.g., pills, tablets) have the advantage of masking or encapsulating bitter tastes, such methods are ineffective for many children because they often cannot or will not swallow pills or tablets. The cutoff for needing liquid formulations typically is between 6 and 8 years of age,[6] but older children (and teenagers and adults) vary greatly in their ability to swallow tablets and capsules.[7,8] In addition, fixed doses are impractical because the dosage often varies according to the size of the child. The Physician

Drug and Diagnosis Audit revealed that 6-year-olds were four times as likely as 16-year-olds to not take their medications as oral solids.[2]

Drugs usually are administered not alone but, rather, as part of formulations that are in either liquid or solid form. Liquid formulations are complex mixtures containing many other components besides the active ingredients; excipients include, but are not limited to, bulk materials, flavorings, sweeteners, buffers, preservatives, and coloring agents.[9] Because masking the bitter taste of medications is a major challenge in formulating liquid medications, drugs are often combined with more pleasant-tasting compounds, for example, sucrose, high-intensity sweeteners, and flavors popular with children, such as bubble gum. Adding both sugars and acids to medication formulations reduces, but does not completely eliminate, the bitterness of drugs.[10] However, frequent use of sucrose-sweetened medicines has been linked to dental caries in children.[11–15] This concern is responsible, in part, for the general decrease in sugar content in prescription medications in recent decades.[16,17]

In contrast, acids remain in frequent use in medicine formulations to improve flavor and to maintain chemical stability.[18] Children like more intense sourness than do adults,[19] so lowering the pH increases the palatability for children, probably more so than for adults, and can contribute to bitter taste masking. Using buffering agents to adjust pH into the acidic range also increases the stability of medications otherwise prone to hydrolysis in liquid formulations.[20] However, adding acids to medications has the potential to cause dental erosion (at pH < 5.5).[18] About half of 97 pediatric medication formulations used regularly and over the long term by children have an endogenous pH below 5.5 and thus are capable of damaging tooth enamel.[18] Citric acid was the most frequently used acid, which raises concerns because citric acid has been linked to tooth erosion due to its ability to dissolve the hydroxyapatite of tooth enamel and dentin.[21,22]

The need for liquids for some children may be bypassed by newer modalities for delivering medications for children. However, solid oral minitablets were refused, spat out, or chewed by half of children younger than 5 years,[23] and chewables and melting tablets trigger bitter taste responses, limiting the compounds amenable to such formulations. In addition, new research suggests that the ingestion of bitter compounds may also act in the gut to elicit nausea.[24] Whether children's encounters with a relatively novel-tasting medication followed by nausea can result in a long-lasting learned aversion to the flavor[25] is an important area for further research.

Although liquid formulations are often the preferred form of oral delivery for infants and young children,[2,20,26] the vast majority of drugs are not commercially available in this form.[26] The need for liquid formulations is expected to rise—most newly approved drugs are not yet labeled for use in pediatric patients, and an appropriate formulation usually is not available unless the drug is approved for that population.[26]

In this article, we draw knowledge from the chemical senses literature, with emphasis on bitter taste research involving animal models and on recent developments in the psychophysical assessment of taste responsiveness in children (see Mennella and Beauchamp 2008[27] for an earlier review), to better understand the nature of bitterness and suggest further ways to make medications more acceptable to the pediatric population. We focus on bitter taste but acknowledge that other sensory attributes (e.g., texture, sourness, or bad odors) also play a role in compliance. We review the set of genes that encode for the known proteins that function as bitter receptors, as well as the cascade of events that lead to multidimensional aspects of taste function, highlighting the role that animal models played in these discoveries. We also summarize psychophysical approaches to study bitter taste both in animal models and in pediatric populations, and we compare and contrast bitter taste

perception between adults and children and identify gaps in knowledge. When appropriate, we reference review articles to direct the reader to the wider literature.

3. Overview of Bitter Taste

Taste is one of the senses through which humans and other animals perceive their environment. One of the primary taste qualities is bitter, a sensation that arises when specific chemicals are detected by specialized receptors in the tongue, as well as other parts of the oral cavity (e.g., throat). In developing effective strategies for reducing the bitter taste of medications, it is important to consider the basic functional architecture of the gustatory system (illustrated schematically in the Figure). We summarize the state of knowledge about bitter taste, from peripheral receptors to the brain, and link this system with perception.

a. Neurobiology of Bitter Taste

i. Peripheral and Central Anatomy of the Gustatory System—The principal sensory organ of gustation is the taste bud, a collection of about 50–100 specialized epithelial cells, some of which serve the role of receptors. Receptor proteins are expressed on the apical membranes of microvilli, which protrude into a pore in the epithelium, where they have access to the oral environment (see segment labeled “Taste Bud” in the Figure). Thus, stimuli must be in solution to adequately reach and stimulate the receptor cells.

The taste buds are bathed in excretions from the sublingual, submaxillary, and parotid salivary glands, as well as from numerous minor salivary glands throughout the oral epithelium. Although there is sufficient evidence that saliva plays a significant role in taste receptor activation by orally applied chemical compounds, its contribution has not been extensively studied. Proline-rich proteins found in saliva can bind with bitter-tasting tannins found in some foods, increasing their acceptability.[28] Proline-rich proteins arise from gene clusters that are interleafed with bitter receptor genes, hinting at a common regulatory mechanism and function.[29] A better understanding of the function of saliva in taste receptor processes may help us curtail the bitterness of medicines.

Taste buds are distributed in distinct fields in the oral cavity (see “Oral” segment on the Figure).[30,31] In the anterior tongue, taste buds are housed in specialized protrusions called fungiform papillae. In the posterior tongue, the taste buds are found in a series of trench-like structures in the lateral margins, referred to as the foliate papillae, and in moat-like structures in the dorsal surface, referred to as the circumvallate papillae. Extralingual taste buds are also found on the soft palate and in the laryngeal epithelium. Each field is selectively innervated by a specific branch of the seventh, ninth, or tenth cranial nerve, which all project to the rostral nucleus of the solitary tract (NTS) in the medulla, where they terminate in a roughly overlapping orotopic fashion.[32–34]

Interestingly, the pathway of gustatory signals through the brain varies somewhat across the mammalian species examined.[35] For example, in rodents and lagomorphs (e.g., rabbits and pikas), taste-responsive neurons in the NTS, in addition to contributing to local hindbrain circuits involved with oromotor and autonomic function,[36–38] project to the parabrachial nucleus (PBN). The projections from PBN neurons bifurcate, with one set terminating in ventral forebrain structures associated with homeostatic functions and affective processes, and the other in the parvocellular subdivision of the ventral posterior medial nucleus of the thalamus, from which neurons send their axons to terminate in the insular cortex’s gustatory zone. In primates, the projections of the taste neurons of the NTS bypass the PBN and terminate in the thalamus, whose cells project directly to taste cortex (see Figure, “Central Nervous System”).[39] Thus, the ventral forebrain in primates receives its taste input from

cortical structures. Many of these pathways are reciprocal, setting the stage for significant feedback to modulate the signals.

Regardless of the different anatomical paths of taste signals through brain in various mammalian orders, the significance of which remains to be understood, in all cases taste signals can be modulated not only in the periphery but also anywhere along the central gustatory pathway. For example, the adage “a spoonful of sugar helps the medicine go down” receives some support from evidence that sucrose can indeed decrease the perceived intensity of quinine, a phenomenon referred to as mixture suppression.[40,41] Although some mixture suppression effects likely have a peripheral origin,[41,42] there are central contributions as well.[40,41] For example, if the sucrose solution is applied to one side of the tongue and the quinine solution to the other, the perceived intensity of the quinine is attenuated despite the stimulation of independent lingual receptor fields.[41] Further, anesthetic block of the nerve that innervates the front of the tongue increases perceived bitterness of quinine applied to the back of the tongue, presumably preventing inhibition arising from anterior lingual taste signals.[42]

ii. Taste Receptor Mechanisms and the T2R Family—There are two general classes of taste receptor mechanisms: the G-protein-coupled receptors (GPCRs), involved in mediating sweet, bitter, and umami taste, and the ion channel receptors, implicated in salt and sour taste.[43–47] The activities of some of these receptors and/or their downstream transduction intermediaries are thermally sensitive,[48–50] making temperature a candidate strategy for modulating the taste of medicine.

All of these receptor proteins are expressed in a variety of tissues in the body.[51–55] For example, the GPCRs that serve as taste receptors are also found in the gut.[51,52,54] This has led to the term “gut taste,” which is more of a metaphor than a reality: as described below, “taste” results not from the receptors themselves but from the downstream neural consequences of the activation of these receptors. Bitter receptors are also expressed in the ciliated cells of the sinonasal epithelium and can trigger immune responses when stimulated with chemical signals from bacteria.[56]

The GPCRs share certain transduction intermediaries in taste receptor cells, such as α-gustducin, PLCβ_2, and TrpM5, which ultimately lead to release of the neurotransmitter (see the “Cell and Molecular” segment in the Figure).[57] In some cells, the G-protein subunit α-gustducin helps mediate responses to both bitter- and sweet-tasting ligands.[58,59] Because GPCR transduction signaling components are shared by both bitter and sweet-tasting ligands, they may not be *selective* targets for decreasing the bitterness of medications. However, although to our knowledge it is untested, the deactivation of these signaling components on a temporary basis could prove useful because even if sweetness is potentially attenuated, the decrease in bitterness could lead to an overall increase in the acceptability of the medicine.

The T2R family of taste receptors was discovered a little more than a decade ago.[60,61] It consists of about 25 GPCRs that serve as the principal receptors for mediating bitter taste. Although many of the receptors remain to be de-orphaned (i.e., determine which ligands activate them), most T2Rs studied have binding profiles that involve several different bitter-tasting ligands.[62,63] Likewise, a given bitter-tasting ligand can activate more than one T2R.[62,63] As might be expected, there are some genetic variants in the receptors within and across species.[63] For example, a subset of the population, classified as “nontasters,” cannot detect the presence of the compounds propylthiouracil (PROP) and phenylthiocarbamide (PTC) at moderate concentrations that all others, referred to as “tasters,” find exceptionally bitter.[64] The nontaster phenotype is due to a haplotype involving polymorphisms at three

amino acid positions in the hT2R38 protein, which is known to bind with these compounds.[65] Likewise, genetic variants within another cluster of bitter receptor genes affect the ability to perceive the bitterness of quinine,[66] a bitter chemical used in the past to treat malaria. Thus, variation in the compliance of children to ingest particular liquid medications could be attributable to potential polymorphisms in these or other T2Rs that have yet to be revealed.

Developing research indicates that receptors for stimuli generating different taste qualities are not co-expressed in taste bud cells.[44,45,47,60,67] Thus, if a taste bud cell expresses the T1R2+T1R3 receptor responsible for mediating sweet taste, it will not express any of the T2Rs that serve as the receptors for bitter-tasting ligands. Although rodent studies first indicated that virtually all T2Rs were co-expressed on taste receptor cells responsive to bitter ligands,[60,61] later human studies revealed that most T2R-expressing cells express only a subset of the T2R members.[63] Nevertheless, a consistent systematic pattern to this expression has not been identified. This lack of co-expression sets the stage for the flow of taste information that gives rise to different qualitative taste perceptions, although there is plenty of opportunity for convergence in the transmission of the signals through the brain.

iii. Neural Response Profiles to T2R Ligands—In addition to overlap among ligands for receptors and receptors for ligands,[62,63] there is overlapping expression of the T2R members in the subset of taste bud cells responsive to bitter compounds. Surprisingly, however, imaging experiments of intracellular changes in calcium concentration in rat taste bud cells *in situ* in response to bitter stimuli indicate much narrower tuning properties: of the 374 cells tested, 69 responded to at least one of the five bitter ligands in the test panel, and of these, 45 cells responded to only one and 18 responded to only two.[68]

Because single axons from a taste nerve branch are close to the tongue and innervate more than one taste cell, any selectivity present in taste receptor cells could be lost by early convergence in the system. The extent to which this occurs at the ganglion cell level remains understudied. Most prior studies used only quinine hydrochloride as the bitter stimulus, rather than a diverse set of bitter ligands. Moreover, the vast majority of peripheral and central electrophysiological results in the literature are based on anterior tongue stimulation, reflecting the contribution of only about 15% of the total taste bud population and circumventing the taste receptor field of the posterior tongue, which has the densest expression of T2Rs.[60] This is due, in part, to the difficulty in effectively perfusing the foliate and circumvallate trenches in the posterior tongue with stimulus solutions in an anesthetized preparation.

Despite these difficulties, two studies stand out in this regard. Frank[69] published the first comprehensive set of findings detailing the response properties of single fibers in the glossopharyngeal nerve. She inserted a pipette into the circumvallate papilla of the rat (rodent tongues have only one circumvallate papilla, vs. ~10 in the human tongue) and tested salts, acids, sugars, and quinine. Although in her prior studies quinine-responsive single fibers in the chorda tympani nerve innervating the front of the tongue responded best to acids and other electrolytes,[70] in this study a set of fibers was identified that responded selectively to quinine and not to the other stimuli. This indicates a segregation of quinine-evoked signals from those of other taste qualities, consistent with the so-called *labeled-line model* of neural coding, in which activity in a given class of neurons is necessary and sufficient for generating a specific taste quality.[71]

In the other study, Dahl and colleagues[72] recorded single-fiber responses in the chorda tympani nerve (anterior tongue) and the glossopharyngeal nerve (posterior tongue) to a panel of bitter-tasting ligands. Not all ligands stimulated the same fibers, suggesting that

signals may be present in the overall peripheral input that permits some discriminability among these particular bitter compounds. This has been taken as evidence for an *ensemble* or *across-neuron model* of neural coding.

Once the signals from the peripheral nerves reach the brain, there is opportunity for further anatomical convergence. From a functional standpoint, the pattern of this convergence is key in terms of how the nervous system represents information about chemical compounds contacting the oral epithelium. Indeed, there is evidence that the breadth of tuning of taste-responsive neurons increases in the brain. However, some narrowly tuned neurons are still present in the population, and it is unclear to which taste function a given neuron contributes. Thus, some neurons might be responsive to the affective valence of the stimulus, whereas others might code for taste quality and contribute to stimulus identification.[73]

The literature on responses of central taste neurons to bitter-tasting stimuli in rodent models is mixed. For many years the bitter stimulus quinine was included in many electrophysiological studies of neuronal taste responses in several central gustatory structures, but despite its potent behavioral effects, neuronal responses were weak or nonexistent—possibly because many studies did not stimulate the posterior tongue. In recent years, however, some more robust responses of neurons in the gustatory zone of the NTS and PBN to a variety of bitter-tasting ligands have been revealed.[74–76] Indeed, a class of neurons has been identified that respond best to bitter compounds and little to compounds associated with other taste qualities.[74,75] Within this class, however, not all bitter compounds are equally effective stimuli for a given neuron. This may be due to idiosyncratic upstream connections originating from the specific T2Rs expressed in the taste receptor cells, or it may represent a fundamental distinction in organizing inputs from subclasses of bitter-tasting ligands. Some of the ionic bitter compounds can also stimulate neurons that respond best to acids and electrolytes, adding another layer of complexity to the unraveling of the neural representation of bitter taste.[74,75]

In a set of recent results using a two-photon imaging protocol to measure cellular calcium responses, anatomically distinct clusters of neurons were found in the insular cortex of the mouse that appeared to respond selectively to taste compounds associated with specific basic taste qualities, including a group that responded only to bitter compounds.[77] The disparity between these findings and the lack of evidence of explicit chemotopy from electrophysiological studies of central neuronal taste responses[71] has yet to be resolved. However, results from an earlier study using a less spatially precise optical imaging technique provide support for some degree of a spatial mapping of taste quality in this cortical region.[78]

From all that we now know about bitter perception and its multiple receptors, it is not surprising that the bitter taste of oral pharmaceuticals is an ongoing formulation problem. The mechanics of bitter taste signaling suggest that it should be amenable to the methods of pharmacology.[79] However, the large number of bitter-tasting compounds and receptors makes blocking bitterness at the receptor level difficult because medicines may have multiple bitter compounds that stimulate multiple receptors, and each receptor may require its own antagonist. As mentioned above, the blockade of second messenger signaling poses problems because several components of the bitter-taste transduction pathway are shared with those mediating sweet taste, and attenuation both bitterness and sweetness may pose practical problems because sweeteners are a commonly used agents to reduce perceived bitterness. Nonetheless, temporary nonselective blockade of these taste transduction pathways could lead to an overall increase in the acceptability of the medicine.

b. Linking the Neurobiology of Bitter Taste to Perception

The discussion above provides a cursory description of the "hardware" of the gustatory system, with a focus on neural mechanisms underlying bitter taste. Most of what we have learned about the molecular aspects of bitter taste transduction has been from experimental animal models, mostly rodents.

However, without data defining the psychophysical properties of various taste compounds and their mixtures, we cannot link the underlying neurobiology with perception. In this regard, animal models are particularly useful because effects of very selective manipulations of the gustatory system can be studied in a highly systematic and quantitative way, in a wide variety of tissues, including the nervous system, as well as in taste-related behavior. In such efforts, however, it is important to be mindful of several interpretive guidelines.[73]

First, when most people talk about "taste," they are actually referring to flavor. Flavor can be considered the perceptual integration of signals from the gustatory, olfactory, and trigeminal systems.[80] To the specialist, however, taste refers to the behavioral and physiological consequences of stimulating taste receptor cells in the oral cavity. Accordingly, the potential for taste stimuli to activate nongustatory sensory systems, including those of a viscerоceptive nature in the cases where the taste solutions are swallowed, must be considered.

Second, perception cannot be measured directly—it must be inferred from behavior. The veracity of that inference depends heavily on the procedure used to measure the behavior, whether studying animals or humans.

Third, taste function is multidimensional. The *sensory/discriminative dimension* encompasses stimulus identification, including the basic taste qualities sweetness, sourness, saltiness, bitterness, and umami. The *affective dimension* involves the hedonic evaluation of taste stimuli, ultimately promoting or discouraging ingestion, which is perhaps most relevant to addressing the unpalatable nature of bitter medicines in children. *Physiological reflexes* are also triggered by taste stimuli, such as salivation triggered by the oral sampling of a lemon. Thus, behavioral outcomes from a given gustatory manipulation need to be interpreted in light of the domain(s) being assessed.

Finally, a neuron's response to an orally applied chemical stimulus does not, in and of itself, reveal the functional domain(s) to which the cell contributes. In this sense, behavioral observations are indispensable in understanding of the neurobiological mechanisms underlying taste function.

4. Behavioral Assays in Animal Models

Although behavioral procedures involving nonhuman subjects are time-consuming and resource-intensive, their value is indisputable because they link the neurobiology of the gustatory system to behavior and, by inference, perception in the same animal model. Rodents are particularly useful animal models for studying taste perception: they are commensal with humans and thus have a similar sense of taste. Animal models also share other similarities with very young children: for both populations, behavior rather than language communicates important information about their sense of taste. The behavioral outcomes from animal models can then be compared with psychophysical results from similar experiments conducted with human subjects, providing a potential bridge between the animal neurobiological data and human taste perception.

The most common behavioral procedure for assessing taste function in animal models (and in young infants, as described below) remains the *two-bottle preference test* in which the

animal is simultaneously presented with two liquid stimuli (e.g., sucrose solution vs. water) for a specified duration. Although these tests provide a reasonable first approximation of an animal's taste responsiveness to a given compound and have the virtue of simplicity, their interpretation is limited because intake and choice can be influenced by nongustatory contributions, most notably, those arising from postingestive events (e.g., satiety or nausea). Over the last several decades, however, a variety of behavioral procedures have been developed that assess taste function more selectively.[81] These procedures could have great utility in testing various strategies for screening drugs in their early stages of development or for modulating the bitter taste of a drug based on more fundamental physiological or molecular research. In this section we briefly summarize each of these methodologies in animal models.

a. Brief-Access Test

The brief-access taste test is an effective way to circumvent the limitations of intake tests by presenting small volumes of taste samples and measuring immediate behavioral responses. Generally, various concentrations of a given taste compound are presented in very brief trials, on the order of seconds, and licking responses are measured with the help of specialized testing devices[82–90]. This procedure is most commonly used to test rats and mice. With normally preferred taste stimuli, such as sucrose, the animals can be tested in either a nondeprived or a food-deprived state, and a monotonic increase in licking as a function of concentration is generally observed. With aversive stimuli, such as bitter-tasting ligands, animals are tested in a water-deprived state, and a monotonic decrease in licking as a function of concentration generally occurs.

These responses are sensitive to gustatory manipulations. For example, mice in which the gene encoding the GPCR taste transduction intermediaries PLCβ2 and TRPM5 have been knocked out display relatively flat concentration-response curves to sweet and bitter stimuli compared with wild-type controls.[57,91,92] Interestingly, the knockout mice still display some licking avoidance of very high concentrations of certain bitter-tasting compounds, such as quinine or denatonium, suggesting an alternative high-threshold taste transduction pathway(s) for these ligands that is independent of $PLC\beta_2$ and TRPM5.[91,92] Although the brief-access test does not assess taste quality perception per se (e.g., NaCl, citric acid, and quinine all produce decreasing licking functions), it is an effective measure of an animal's affective responsiveness to a taste stimulus and has great potential utility for testing masking agents and other strategies to attenuate the aversiveness of medicines.

b. Taste Reactivity

Many animals, including rodents and humans, display reflex-like oromotor responses to taste stimuli,[93] which has been termed *taste reactivity*.[94–97] This has been best studied in rats in which taste solutions are delivered directly into the oral cavity through surgically implanted cannulas. Normally preferred taste stimuli, such as sugars, elicit tongue and mouth movements directly proportional to the concentration of the solution. These are collectively referred to as *ingestive behaviors*. Normally avoided taste stimuli, such as quinine, elicit gapes, chin rubs, forelimb flails, and head shakes directly proportional to the concentration of the solution, and all of these are generally accompanied by active fluid ejection. These are collectively referred to as *aversive behaviors*. Transection of the glossopharyngeal nerve, which innervates the taste buds of the posterior tongue where T2Rs are densely expressed, virtually eliminates the characteristic aversive oromotor responses to intraorally delivered highly concentrated quinine solutions,[98–100] which return when the nerve regenerates.[100]

Although bitter taste stimuli are often aversive, not all aversive tastes are bitter. Accordingly, taste reactivity does not assess taste quality but rather provides information about the acceptability of various taste stimuli. Nonetheless, these procedures could contribute significantly to developing ways to increase medication palatability.

c. Conditioned Taste Generalization and Discrimination

These procedures can more selectively assess taste quality independent of the inherent hedonic characteristics of the stimulus, by establishing a taste stimulus as a conditioned signal. For example, with the *conditioned taste aversion procedure*, commonly used in rodents,[86,90,101,102] the ingestion of a specific taste stimulus is paired with administration of an agent that produces temporary visceral malaise (presumably nausea). On subsequent occasions, the animal will avoid ingesting the conditioned stimulus and others that have a similar qualitative taste, a phenomenon called *generalization*. When the test array includes sucrose, quinine, NaCl, and citric acid, inferences can be made about how sweet, bitter, salty, and sour the conditioned stimulus is. Although intake compared with nonconditioned control animals is often the primary dependent measure, brief-access tests and taste reactivity measures can also be used.

One limitation of the use this paradigm to assess qualitative characteristics of naturally aversive taste stimuli is that they are already unconditionally avoided. However, operant conditioning procedures can circumvent this shortcoming. In these procedures, a small volume of a taste compound serves as a cue in the presence of which a specific response is rewarded or punished. For example, using a specially designed gustometer, Grobe and Spector[103] trained one group of thirsty rats to lick a specific drinking spout after sampling sucrose (the standard stimulus) and a different spout after sampling quinine, citric acid, or NaCl (the comparison stimuli). If the rats responded correctly, they were rewarded with water; if not, they were punished with a time-out. Three other groups were trained with quinine, citric acid, and NaCl, respectively, as the standard stimulus and the remaining compounds as the comparison stimuli. Concentrations of all stimuli were varied, rendering intensity cues irrelevant. After all four groups learned the task, a test compound was randomly interjected during the taste trials. By observing which spout each animal went to after sampling the test stimulus, the experimenters were able to infer taste quality of the sample using the response profiles across all four groups: sweetness (sucrose standard group), bitterness (quinine standard group), saltiness (NaCl standard group), and sourness (citric acid standard group).

A similar procedure can test how well rats and mice can discriminate between two specific compounds. There has been some debate about whether animals can discriminate among bitter-tasting compounds. As noted above, the co-expression of T2Rs in taste receptor cells, as well as their somewhat broad tuning profiles, predicts poor discriminability, whereas the calcium responses of taste bud cells predict good discriminability. The response profiles for central taste neurons can be used to support either prediction. Spector and Kopka[104] tested whether rats could discriminate between quinine and denatonium, for which calcium imaging suggested a high degree of discriminability. The procedure was similar to the one described above: rats were rewarded for licking one spout when quinine was delivered and for licking the other when denatonium was presented; incorrect responses were punished with a time-out. These rats could not be trained, but did subsequently learn to discriminate quinine from KCl.

A second group of naive rats were first trained to discriminate quinine from KCl; then denatonium was substituted for quinine, and performance remained unperturbed on the very first session, suggesting that denatonium and quinine share similar qualitative properties. To show that any stimulus substitution does not necessarily result in unaltered performance,

Spector and Kopka substituted NaCl for denatonium. In this case, performance dropped to chance levels on the first session and then subsequently improved across sessions as the animals learned the new discrimination task. Finally, these same highly trained rats were tested on the quinine vs. denatonium task, and their performance remained at chance over 15 test sessions. Accordingly, if rats can discriminate quinine from denatonium, it is likely very difficult, suggesting that the two compounds produce a unitary qualitative taste perception that one could perhaps call bitterness. Whether other bitter-tasting ligands can be discriminated from one another remains to be tested. On a more conceptual level, failure to discriminate is always more compelling than is success, provided learning and intensity effects can be ruled out, because it suggests that an identity relation exists somewhere along the sensory neuraxis.

5. Behavioral Assays in Children

A major challenge in formulating pharmaceuticals for children's palates is the identification of methods to assess the acceptance of the taste of the medicines, once they are approved, and to determine in the long term which methods yield data that predict adherence/compliance to medication regimes.[105] When conducting research in children, several methodological issues need to be addressed.

First, young children are more prone to attention lapses and have shorter memory spans compared with adults. Therefore, any method relying on sustained attention that places demands on memory could yield spurious findings. Second, because young children tend to answer questions in the affirmative, a forced-choice categorization procedure is generally preferred. Age-appropriate tasks embedded in the context of a game that are fun for children and minimize the impact of language and the stage of cognitive development, are particularly effective. Third, before actual testing and after a period of acclimation, the experimenter should ascertain whether the child comprehends the task. Training tools are needed to determine whether a given child has the ability to do the task. Reproducibility of the measures over time should be built into the design of the study. All of these special features must be considered when developing sensory methods for children.

A variety of psychophysical methodologies have been employed to assess taste perception and preference throughout infancy, childhood, and adolescence.[106] The method chosen depends on the objective of the study, as well as the age (and, in turn, cognitive and language abilities) of the participants under study. These psychophysical studies on taste provide data relevant to two separate aspects of sensation: (1) the *sensitivity* of the system to chemical stimuli and (2) the *hedonic valence*, or pleasantness, of the sensation.[107,108]

The century-long legacy of experimental research in taste has revealed that, like the other senses (sounds,[109] smells,[110,111] and irritants[112]), children live in different sensory worlds than do adults. These age-related differences are especially striking for taste. Within hours after birth, infants have been shown to prefer sweet and umami tastes[113–115] and to reject bitter-tasting liquids,[116] although adult-like sensitivity to salt does not emerge until the infant is approximately four months of age.[117] Their dietary likes and dislikes provide further evidence of their stronger liking for foods and beverages that taste sweet,[118] salty,[119] and, in some cases, sour[120] and their profound dislike of all that tastes bitter. Children's heightened liking for sweets and salts, relative to adults, probably reflects the need for energy or minerals, respectively, during periods of maximal growth, since many foods rich in energy (e.g., mother's milk, fruits) taste sweet. Thus, it is not surprising that many pediatric formulations taste sweet.

The Table provides an overview of some of the psychophysical tools used to study bitter taste in children (for more thorough review that includes the other basic tastes, see Forestell

and Mennella 2013[106]). For preverbal children, the tools often focus on reflex-like responses (e.g., orofacial responses) or consummatory responses—many of the experimental paradigms for this age group are similar to those used in animal model studies,[85,94,116,121–123] as reviewed above. Because virtually all of these measures can be associated with acceptance or rejection, they presumably involve a hedonic component. At least for human infants, sensitivity and hedonics are difficult to distinguish.[108] For older children, the psychophysical tools are more complex, but very little research has established at what age children can reliably perform these tasks.

a. Taste Reactivity

Some of the earliest investigations on taste in infants involved videotaping infants and then characterizing their oromotor reflexes when taste stimuli were placed on the tongue or in the oral cavity.[114–126] In 1988, Oster and Rosenstein[115] developed a method for describing orofacial responses with Ekman and Friesen's[127] anatomically based Facial Action Coding System (FACS), which can dissect virtually any facial expression into its constituent action units (AUs). Video records are often analyzed in slow motion[97] to quantify the actual number of affective reactions infants express to a taste stimulus, as a measure of valence and intensity.[128] This method requires trained individuals (preferably certified in FACS) to analyze the video images and establish reliability across scores,[125] which can be time-consuming and costly.

b. Brief-Access Tests: Intake and Suckling Methods

Ingestive and suckling responses have been used successfully to study response patterns as a function of individual and age-related differences in taste perception. Methods include delivering small quantities of taste solutions directly to the tongue or providing brief access to multiple bottles in succession that contain various taste or diluent solutions.[113,129–132] In some cases, a transducer was embedded into the nipple of the bottle to measure the patterning of suckling in response to the tastant.[133,134] In other cases, infants are tested on repeated days for their acceptance of a food (e.g., cereal) that differs in taste quality,[125,128] which requires controlling for a number of variables, including time of day and time since the infant was last fed, and ensuring that appropriate controls are built into the study design. One can then infer from this research that infants detect a bitter taste solution (e.g., urea solutions), and reject it more than the diluent, if they consume less (or suck less) of the bitter taste solution than of the diluent solution.[130,132]

c. Forced-Choice Tracking Procedure/Thresholds

Various methods have been used to measure how sensitive a child is to a particular tastant (e.g., taste thresholds) and whether there are individual differences. Perhaps the most widely studied taste trait relates to the genetically determined ability to taste compounds containing an N–C=S (thio) group, such as phenylthiocarbamide (PTC) and its chemical relative propylthiouracil (PROP), in human populations.[10–14] As mentioned above, these chemicals taste bitter to "tasters," whereas "nontasters" either cannot taste them or require high concentrations to recognize their presence.

A variety of methods have been used to assess sensitivity to PROP and/or PTC.[135–138] Often, these include forced-choice procedures embedded in the context of a game. Based on the procedures of Anliker and colleagues (1991),[139] children were presented, in succession, with samples of water and then three increasing concentrations of PROP (56, 180, and 560 μM) and were asked to taste the sample without swallowing.[137,140,141] If the solution tasted like "water" or "nothing," then they were asked to give the sample to Big Bird, a popular television character. If the sample tasted "bad," "yucky," or "bitter," children were asked to give it to Oscar the Grouch so he could throw it in his trash can. Children were grouped by

the concentration of the first sample, if any, that was given to Oscar the Grouch. Children who were heterozygous at the *TAS2R38* gene locus—that is, had one "taster" and one "nontaster" allele—were more sensitive to the taste of PROP than were heterozygous adults. The thresholds of heterozygous adolescents were intermediate,[140] and homozygous children and adults showed no difference in threshold.

In other studies, children were presented with a series of pairs of solutions: water paired with an aqueous tastant (i.e., paired comparisons). In some cases the aqueous tastants increased in concentration with each pair presented, and the child was asked to indicate which sample of the pair contained the tastant or tasted stronger. The lowest concentration successfully detected in one or two consecutive trials was recorded as the detection threshold.[142]

d. Scaling Procedures

Various types of scaling methods (i.e., methods in which sensations to varying concentrations of suprathreshold stimuli are quantified) have been used to determine children's preferences and sensitivity to tastes. Depending on age, children are presented with a line or other type of scale that contains pictorial or verbal descriptors in a graded order. Although there has been no systematic determination of what scaling test is most appropriate for children at what age, some researchers have concluded that use of scales in children younger than age 5 can be problematic because they have not mastered the ability to rank things in order of magnitude.[143]

A variety of methods, including spontaneous verbal reports following dosing, time required for medication intake, 10-cm visual analog scales, and hedonic face scales, are used by pharmaceutical companies, marketing research firms, and other investigators when testing children.[144] Several different 5-point hedonic scales have been developed to assess taste acceptability of pharmaceuticals.[145–149] These scales typically consist of five different facial expressions accompanied by written labels and are used to evaluate children's hedonic responses after tasting one medication at a time. Davies and Tuleu[150] searched PubMed to identify 30 papers assessing medication palatability in children dating back to 1984 and found that half of the studies used a hedonic scale to rate palatability and that participants included children as young as 3 years. Although 5-point scales typically were used,[149] scales ranged from 2 points[151] to 10 points.[152] The use of such scales in young children is potentially problematic, as it is not clear at what age children begin to use the entire scale versus just the two extremes.[105] To date, only a few studies have examined the validity and reliability of hedonic scales in young children. We highlight some of these studies and how their findings provide insight into whether such methods are even valid for pediatric populations.

Sjovall and colleagues[153] compared spontaneous verbal judgments and a 5-point facial hedonic scale in children given five different penicillin formulations. Although both methods successfully discriminated between pediatric formulations when used with older children, for children 6 years and younger spontaneous verbal assessment discriminated between formulations better than did the facial hedonic scale.

Leon and colleagues[154] examined the reliability and validity of facial hedonic scales in children whose ages ranged from 4 to 10 years. Children in the study tasted biscuits covered with different flavors of jam. Children 4 and 5 years old rated the jams using a 2-point hedonic face scale (like vs. dislike), whereas older children rated them using a 4-point hedonic face scale (like very much, like, dislike, dislike very much). For children younger than 5 years, intersession repeatability of results with the hedonic scale was poor (Kendall correlation = 0.18) and did not correlate with other measures of preference in the same

children. In contrast, children older than 5 years could reliably use the 4-point hedonic scale, and results correlated with other measures of preference. These studies illustrate the difficulty of using hedonic scales in young children.

e. Application of Methods to Study Bitter Taste in Children

Some children refuse to take bitter medicines, whereas others comply readily.[2] Likewise, not every child (or adult) is equally sensitive to the taste of bitter compounds.[137] Many children are more sensitive to bitter tastes than are adults.[131,137] However, because of the paucity of research on the ontogeny of bitter taste sensitivity, we do not know the full extent of the differences in perception between adults and children and how that relates to individual genotype. We hypothesize that the substantial degree of sequence diversity and variation that exist in taste receptor genes[155] may underlie individual differences in medication adherence in children related to taste. Although these individual differences arise for a variety of reasons (e.g., temperament,[156] experience,[157] ethnicity/race[158]), the best-known example is person-to-person genetic variation. As described above, variations in perception of the bitter compound PROP are due in large part to “taster” and “nontaster” alleles of a particular bitter receptor.[65,159] Allele frequencies for this gene differ markedly by race; for example, high sensitivity to the bitterness of PROP and related compounds is more common in African populations.[155]

A recent study explored the relationship between genotype of one of the 25 bitter receptor genes (*TAS2R38*) and medication history.[160] Children younger than 10 years who had at least one taster (P) allele (PP or AP genotype) were more likely to have taken medicine in solid formulation than were nontaster (AA genotype) children. We hypothesized that the resistance to taking bitter liquid formulations may relate to compliance and that bitter-sensitive children may be resistant to taking bitter liquid formulations and motivated to try medicine in pill form as an alternative. Although children were genotyped for only one of the 25 known bitter receptors, alleles of this particular receptor may be a proxy for general taste ability,[138] or bitter receptor genes may occur in tightly linked clusters[60] such that genetic variation in this receptor may relate to variation in other receptors. This particular receptor may also respond more broadly than previously understood—drugs commonly used in children’s medications have not been widely tested in assays designed to understand such receptor-ligand interactions. Further study of the relationship between *TAS2R38* genotype and liquid formulation intake and compliance is warranted.

Recent research has revealed that cell-based assays are imperfect proxies of the human taste response. For example, *TAS2R38* has three variant sites that give rise to several taster and nontaster haplotypes. When cell-based assays[159] of these haplotypes are compared with studies of people with those same haplotypes,[141] there is agreement in many cases but not in all, especially for variants that may directly couple with the G protein. This study highlights the need for psychophysical as well as cell-based methods to understand the genotype-phenotype relationship for taste receptors.[141]

Research to further characterize how taste receptor genotype and other aspects of taste phenotypes relate to pediatric medication formulation and compliance is necessary to help us develop better medicines for pediatric populations. Such research could be incorporated into pediatric clinical trials, to help understand individual compliance during the trial and to expand our understanding of the role of taste genetics in behavioral choices. Because children are more bitter-sensitive than are adults, and age-related changes in bitter perception are more common for people with particular genotypes, we need to study both adults and children and take genetic variation into account when interpreting the results.[160] Although we have studied only a few examples of how bitter receptor genotype can affect bitter perception,[66,159,161–164] genotype, like age, it is an important determinant of

perception and should be considered in all methods to evaluate the taste of medicine and compliance.

Many investigators are developing a new generation of molecules to inhibit bitterness.[79] However, there are very few peer-reviewed studies on their effectiveness in adults (reviewed in Roy 1997[165]), and to our knowledge, only one study, conducted in our laboratory, has examined children.[166] Nevertheless, because of the age-related differences in bitter taste perception, we suggest that research aimed at reducing the bitterness of medicine, such as evaluating the effectiveness of bitter blockers, should directly involve children rather than extrapolating from data collected from adults.

6. Artificial Sensor Systems

There is much debate in the literature on whether artificial sensors can be successful substitutes for the human palate and replace the use of sensory panelists, since use of the latter is problematic in industry "due to the potential toxicity of drugs and subjectivity of taste panelists, problems in recruiting taste panelists, motivation and panel maintenance … when working with unpleasant products."[167] Furthermore, because FDA-unapproved drugs cannot be taste tested, use of artificial sensors, it has been argued, can provide important data regarding the taste of these drugs.[167,168]

These artificial sensory devices typically are arrays of sensors, called "electronic noses" for arrays of gas sensors and "electronic tongues" for arrays of liquid sensors. Often these devices are designed to analyze the levels of various ingredients composing a fluid mixture and in a variety of applications involving product quality control.[169] But in recent years, these devices have been used as an analytical gustatory tool in evaluating pharmaceuticals.[167,170–173] It has been argued that this approach, whose advantages include its speed, relatively low cost, and lack of risk, will help develop more palatable pediatric formulations.[174–177]

Nevertheless, whether such artificial sensory systems will lead to significant insights that will address the heart of the problem in practice remains to be seen. Given the numerous and varied components of peripheral and central mechanisms involved in the mediation of bitter taste (summarized in the Figure), the ability of an artificial sensor to model and predict the properties of this complex biological system is questionable. Thus, the utility of the electronic tongue to offer meaningful guidance in the development of strategies to increase the palatability of pediatric formulations is likely to be limited to simply providing a detailed analysis of the chemical constituents in the mixture. However, it is quite possible that, since this is an active area of research, these devices might be more useful in the future.

8. Conclusions

Like other sensory systems, taste is experienced through a "sensory window" that changes with age and experience and is partially defined by genetics. Children have well-developed sensory systems for detecting tastes, as well as smells and chemical irritants, and their rejection of unpalatable medications reflects their basic biological preferences for sweet, salty, and, to some extent, sour tastes and rejection of bitter tastes. Sugars, salt, acids, and other substances help reduce the perceived bitterness of several pharmaceuticals. Although adding pleasant flavor volatiles such as bubble gum may also help induce children to consume a medicine, such volatile compounds are often not very effective in suppressing the strong bitter tastes associated with many medications.

This aversion to bitter creates a roadblock for oral formulations; undesirable chemosensory characteristics can hinder the acceptance and usefulness of many beneficial, safe, and

efficacious drugs. The unpleasant taste of a medicine is often a sensory expression of its pharmacological activity; in many cases, the more potent the drug, the more bitter it will be.[178] The more bitter, the more likely the drug will be rejected. Better-tasting medications may go a long way toward enhancing the ability of pediatric patients to adhere to drug therapy, especially when failure to consume may do harm and, in some cases, be life threatening.[179] Thus, a primary challenge is to reduce the bitterness and other off flavors of pediatric formulations.

Adult panelists who are sensitive to the pediatric palate, new techniques involving animal models, and even electronic detection devices are among the tools that can help evaluate the palatability of medications and predict compliance among pediatric populations. Further development of and consensus regarding which psychophysical tools are valid and appropriate for use with children will provide a better understanding of the sensory world of the child. Testing multiple strategies will help us refine methods that may be used to assess acceptance and compliance/adherence by pediatric populations of varying ages, which will allow for comparisons across studies. These methods then can be applied to clinical trials to obtain data that can help predict initial acceptance versus long-term compliance of a medication, and how medication usage and disease state modify bitter taste perception of the drug in children. While much of the research will by necessity focus on taste testing without swallowing, there are also bitter receptors in the back of the throat[180] that may be engaged primarily during swallowing of the liquid medication. The effect of these receptors on taste acceptance can be studied during clinical trials in which children not only taste but also swallow medicine.

While progress has been made in our current understanding of bitter taste, it is far from complete, and new ways to reduce the bitterness of certain medications may yet be discovered. Most of our knowledge on the neurobiological mechanisms of taste has been derived from animal models in which the gustatory system can be invasively manipulated and studied. As discussed in the preceding pages, a variety of behavioral techniques can be used to link taste perception to its underlying neurobiological processes. Accordingly, these model systems can be exploited to evaluate potential strategies to safely and effectively attenuate bitterness. Such an approach, coupled with psychophysical assessment of taste function in children, and ultimately clinical testing, should increase the chances of finding solutions to what has been the vexing problem of bitter taste reducing drug acceptance and compliance in pediatric populations— understanding bitterness better may take the guesswork out of improving formulations.

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CONFLICT OF INTEREST STATEMENT

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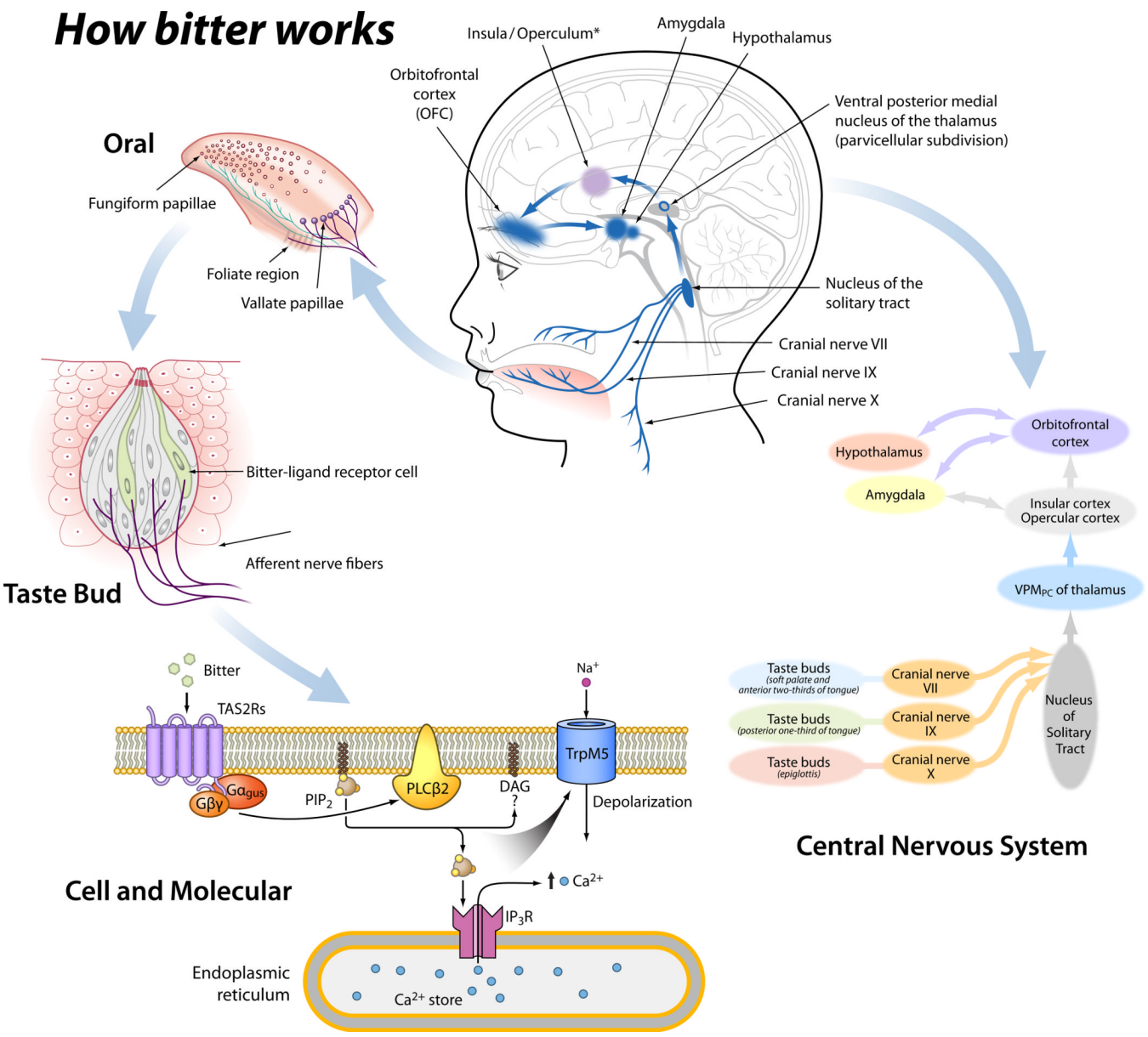

Figure.

How Bitter Works: the process of bitter perception. The generation of bitter taste starts when a bitter compound enters the oral cavity, where the ligand binds to a T2R G-protein coupled receptor expressed in the apical membrane of receptor cells found in taste buds, triggering a cascade of signaling events, leading to the release of neurotransmitter that activates an afferent nerve fiber that transmits the signal via the cranial nerve to the brain. Taste buds are distributed in distinct fields in the oral, pharyngeal, and laryngeal epithelia, with each field innervated by a different cranial nerve branch. Only the taste buds on the tongue are depicted in the figure. The taste buds of the laryngeal epithelium are thought to be involved more with protection of the airways. Taste receptors have also been identified in a variety of nongustatory tissues, such as the gut, where they have been proposed to play a role in nutrient and toxin sensing. The taste signals course through the brain and provide input to circuits that subserve various functions, such as oromotor and physiological reflexes, discriminative perception, and affective processing. The figure illustrates the complexity of

the mechanisms intervening between the application of the bitter stimulus and the generation of the behavioral response, providing a variety of potential targets for strategies to modulate the bitterness of medications. VPM_{PC}, ventral posterior medial nucleus, parvocellular subdivision. *The insula/operculum is actually lateral to the sagittal plane of section shown. Cell and molecular segment adapted from Finger and Kinnamon (2011).[53]

Table

Examples of types of psychophysical tools used to assess bitter taste and medication palatability in pediatric populations.

Method	Age of Subjects	Measures	Outcome Measures	Key References
Facial reactivity	All ages, but facial reactivity as an indicator becomes less reliable with age[181]	The number of affective reactions infants express to a taste stimulus is quantified as a measure of the valence and intensity of an affective reaction. Facial expressions are dissected into constituent action units (AUs) via slow-motion video analysis by trained raters.	Bitter solutions elicit upper and midface Aus (including cheek raises (AU 6) and gaping (AU 26 and AU 27)).	Oster and Rosenstein 1988[115]; Mennella et al. 2009[128]; Forestell and Mennella 2012[125]
Brief-access tests	Infancy (<1 year)	Infants are provided with brief access to two or more bottles in succession containing various bitter-tasting liquids or diluent.	Decreased intake to bitter taste.	Desor et al. 1975[132]; Kajiura et al. 1992[130]
Brief-access tests, multiple days	Infancy (<1 year)	Infants are fed food on multiple occasions; the days differ in the taste of the food presented.	Decreased intake to bitter-flavored relative to plain cereal.	Mennella et al. 2009[128]
Suckling response	Infancy (<1 year)	Patterning of suckling response measured while infant is feeding tastant versus diluent solutions; transducer may be embedded in nipple of bottle.	Retardation of suckling to bitter taste.	Kajiura et al. 1992[130]
Suprathreshold taste thresholds	Children ≥3 years of age	Subjects tasted (but did not swallow), solutions of PROP in ascending concentrations, rinsing with water before and after each tasting. Subjects are then classified into groups based on which concentration, if any, tasted bitter.	Variation in sensitivity to PROP related to *TAS2R38* genotype and children's food likes.	Anliker et al. 1991[139]; Mennella et al. 2005[137]
Scaling methods	Children ≥3 years of age	A variety of scaling methods are used during taste testing to evaluate children's hedonic responses after tasting one solution at a time. Typically, the child is presented with a line or other type of scale that contains pictorial (e.g., faces ranging from frowns to smiles) or verbal descriptors to evaluate stimuli in a graded order.	• Children (4–11 years) with kidney disease rated the taste of two different pulverized calcium channel blockers on a 5-point hedonic face scale to determine most palatable drug.[148] • Children (4–8 years) rated oral suspension of four antibiotics using a 5-point hedonic face scale to determine most preferred drug.[149] • Children (5–8 years) rated four antimicrobial agents	Powers et al. 2000[149]; Angelilli et al. 2000[145]; Milani et al. 2010[148]; Guinard 2001[143]

Method	Age of Subjects	Measures	Outcome Measures	Key References
			using a 10-cm line with face labels placed above the line at approximately 0, 2.5, 5, 7.5, and 10 cm to determine the most palatable drug preparation.[145] • Caveat: unclear at what age children can comprehend these tasks.[143]	