Why Taste Is Pharmacology

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Abstract

The chapter presents an argument supporting the view that taste, defined as the receptor-mediated signaling of taste cells and consequent sensory events, is proper subject matter for the field of pharmacology. The argument develops through a consideration of how the field of pharmacology itself is to be defined. Though its application toward the discovery and development of therapeutics is of obvious value, pharmacology nevertheless is a basic science committed to

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R. K. Palmer, G. Servant (eds.), *The Pharmacology of Taste*,
Handbook of Experimental Pharmacology 275, https://doi.org/10.1007/164_2022_589

examining biological phenomena controlled by the selective interactions between chemicals – regardless of their sources or uses – and receptors. The basic science of pharmacology is founded on the theory of receptor occupancy, detailed here in the context of taste. The discussion then will turn to consideration of the measurement of human taste and how well the results agree with the predictions of receptor theory.

Keywords

Pharmacology · Receptor theory · Taste · Taste discrimination · Taste intensity

1 Introduction: Paradigms for the Study of Taste

We see the world in terms of our theories.
– Thomas Kuhn, The Structure of Scientific Revolutions

In his landmark book *The Structure of Scientific Revolutions* (Kuhn 1962), Thomas Kuhn portrayed the advance of science as a process of transitioning through paradigms-models of the universe and how it operates. A scientific paradigm often is described as a world view, a lens through which natural phenomena are observed and interpreted. For the scientist, the paradigm defines the questions to be asked, the problems to be solved, how and what to measure – the independent and dependent variables – and how to analyze and interpret data. Thus, scientific "operations and measurements are paradigm-determined" (Kuhn 1962). Two scientists, each examining the same phenomenon from the perspectives of differing paradigms, potentially will arrive at very different conclusions about what they observe. Such an outcome might be due to different methods of measurement, different definitions of independent and dependent variables, or even more fundamentally, differing notions of causality.

Here, as elsewhere (Palmer 2007, 2019), the study of the collective phenomena conventionally referred to as "taste" will be presented as a study from the perspective of the paradigm of pharmacology. However, this is a relatively new approach to the study of taste, and currently not predominant. Taste always has been regarded as a sensory perceptual event, and the leading experimental paradigm for investigating sensory phenomena of any kind has been, and remains, psychophysics. Pharmacology studies the functional relationship between receptors and the ligands that occupy them, and how this relationship translates to changes in the functions of biological systems, including behavior. The goal of psychophysics is to obtain quantitative relationships between physical stimuli that impinge upon the nervous system and the subjective sensations and perceptions that follow. The paradigms of pharmacology and psychophysics are vastly different, each evolving from divergent epistemological lineages.

In some cases, the pharmacological and psychophysical techniques used to investigate an aspect of taste essentially are equivalent and, accordingly, generate

equivalent data; but the pharmacologist and the psychophysicist will have different explanations to account for the results. Taste discrimination experiments are representative of these cases. There are, however, situations where psychophysical experimental approaches to the study of taste result in datasets and conclusions that appear contradictory to expectations set by the paradigm of pharmacology. The psychophysics of taste intensity, particularly as it has been measured using intensity magnitude rating scales, exemplifies this latter case and will be addressed in this chapter.

2 The Purview of Pharmacology

It might strike the reader as peculiar that taste be called "pharmacology." After all, taste is a sensory perception, associated with enjoyment of foods and beverages, avoidance of unpleasant and potentially harmful substances, and quality of life. Taste guides ingestion. The ways in which taste has been studied have focused on the sensory event, whether it be detection or intensity of the experience.

Pharmacology, on the other hand, is associated with medical science. The history of pharmacology is tightly interwoven with the study of medicine. The first pharmacology programs at academic universities were founded on the study of therapeutics. John Jacob Abel, the first professor of pharmacology in the USA, formed his pharmacology department within the department of materia medica at the University of Michigan (Parascandola 1992). Moreover, application of the principles of pharmacology has built the entire engineering process of drug discovery in the pharmaceutical industry.

Nevertheless, it is the position of the editors of this volume, and indeed the raison d'etre for this volume, that the study of taste fits well within the domain of the field of pharmacology. To launch the argument, some definitions first are needed.

2.1 Definitions of Pharmacology

There is no shortage of differing opinions on what, or what should, constitute the field of pharmacology. The introduction of taste as a subject for pharmacological interrogation presents a prime opportunity to more clearly define what pharmacology is. In the current context, it would be most instructive to consider what a major pharmacology society considers to be the subject which unites its members. The American Society for Pharmacology and Experimental Therapeutics (ASPET) is a scientific society, founded by John Jacob Abel, dedicated to the science of pharmacology and its applications to therapeutics. The Society defines pharmacology as follows:

> Pharmacology is the science of how drugs act on biological systems and how the body responds to the drug. (https://www.aspet.org/aspet/education-careers/about-pharmacology, last accessed 2022 January 17)

Pharmacology is comprised of two major subdisciplines: pharmacodynamics and pharmacokinetics. Pharmacodynamics refers to the intermolecular reactions which underly the response to a drug, the level at which chemistry is joined to biology. Pharmacokinetics is the tracking of a drug through its time course of activity in the body, and thus ultimately how much of the drug originally administered will remain in its active form at the receptor compartment, the site of pharmacodynamics. Knowledge of the processes encompassed by both pharmacodynamics and pharmacokinetics is necessary to achieve a full understanding of "drug action." The receptors that mediate taste responses, expressed where they are in the microvilli of taste cells on the surface of the tongue (Yang et al. 2020), essentially are directly exposed to the chemicals with which they interact, and therefore "tastant action" is determined almost entirely by pharmacodynamics.

"Drug" is defined by the United States Food and Drug Administration as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals." (https://www.fda.gov/industry/regulated-products/human-drugs#drug, last accessed 2022 January 17). Tastants generally are not used to remedy a disease state (though therapeutics certainly can generate a taste response), and the FDA distinguishes substances that are used for stimulating taste into a different, non-medical category. The FDA definition of drug also applies to recreational drugs, which are used intentionally to affect the function of the central nervous system (and consequently behavior), but explicitly excludes food, and by extension, taste stimuli. But the FDA's definitions are designed to clarify how categories of substances will be regulated for their specific marketed or recreational use.

If the chief objective of the field of pharmacology is to study exogenously applied chemicals that are defined as therapeutics and other agents of medical interest, then it is an applied science – the discovery and study of therapeutics to benefit medical science. There would be little room to include the study of taste in such a field.

However, the famous text *Goodman and Gilman's The Pharmacological Basis of Therapeutics* has acknowledged since its first edition (1941; Brunton et al. 2017) that "A drug may be broadly defined as any chemical agent that affects living protoplasm, and few substances would escape inclusion by this definition." (Rivera and Gilman 2017). Furthermore, the ASPET publication Journal of Pharmacology and Experimental Therapeutics, the first American pharmacology journal, also founded by John Jacob Abel, defines their mission as providing "broad coverage of all aspects of the interactions of chemicals with biological systems. . .," and then proceeds to list a multiplicity of biological systems and related areas of research in which the methods and principles of pharmacology are applied (which, importantly for this chapter, includes behavior; https://jpet.aspetjournals.org/content/jpet-faqs, last accessed 2022 January 17). These definitions and purposes for pharmacology lift its purview from an exclusive medico-centric perspective.

John Jacob Abel himself unequivocally held the view that pharmacology is a basic experimental science, the growth of which should not be encumbered by, in his

words, "the intrusive demands of practical utility." For Abel, pharmacology is the science that. . .

> . . .tries to discover all the chemical and physical changes that go on in a living thing that has absorbed a substance capable of producing such changes, and it also attempts to discover the fate of the substance incorporated. It is not therefore an applied science, like therapeutics, but it is one of the biological sciences, using that word in its widest sense. (quotes are from (Parascandola 1992)

Many histories of pharmacology emphasize its evolution as an experimental science. Often a path of discovery is traced from the work of Claude Bernard, who systematically narrowed down the site of action for curare to the neuromuscular junction (perhaps Alfred Vulpian deserves more credit, see Cousin, 2002), to John Newport Langley's "eureka moment" of the existence of a finite "receptive substance" that explains the pharmacological competition between curare and nicotine in muscle tissue (Changeux 2020; Limbird 2006; Maehle 2004; Rang 2006). Arrival at the receptor concept was the moment that pharmacology was born. The field of medicine benefited all along the way and has ever since.

Throughout the nineteenth century pharmacologists gained support from university departments of materia medica who were increasingly appreciative of the value of experimental pharmacology to the modernization of medical science (Lees et al. 2022; Lesch 1984). Though the history of pharmacology tightly interweaves with that of medicine, the scientific ancestors and founders of pharmacology primarily were interested in understanding the mechanisms by which chemicals changed physiology (Barrett et al. 2019; Scheindlin 2010). The drive to elucidate the mechanisms at play in the interface between chemistry and physiology produced the discipline of pharmacology, regardless of the sources of the chemicals or their intended use.

Currently there is good reason to regard pharmacology as a basic science which is valued for its broad applications, not just an applied science useful to the field of medicine. Often, the experimentation conducted by pharmacologists neither involves a therapeutic agent nor directly relates to the discovery of one. Instead, the focus of entire research programs in pharmacology can be solely on the mechanisms by which any chemical could directly alter physiology, observable at any level of experimental reduction, seeking lawful relationships of cause and effect. That relationship is the product of the function of receptors whose activities serve to translate chemical information from the external face of the cell membrane to the internal workings of the cell. It was the elucidation of a concept of "receptor" that created the theoretical foundation upon which a basic science of pharmacology has been built. The study of taste, a receptor-mediated biological event, fits well within this realization of pharmacology as a basic science.

2.2 Definitions of Taste

The word "taste" evokes many connotations, and consequently careful consideration must be given to a precise definition of the word as it is used to describe processes under scientific scrutiny. "Taste" has been studied from the most reductive examination of cellular and molecular events to emergent phenomena of conscious perception. There are different aspects of the concept of "taste" that determine the dependent variables to be systematically examined and how experimental results will be interpreted.

Perhaps the most familiar aspect of taste is that of a tastant's qualitative properties (Palmer 2019), exemplified by the question "what does this taste like?" The question implies a comparison between the substance of interest and a standard tastant previously experienced. By current consensus, "sweet," "bitter," "salty," "sour," and "umami" are the five taste qualities basic to the concept of "taste" (Beauchamp 2019; Erickson 2008), and common representative standards for these categories are sucrose, quinine, sodium chloride, citric acid, and glutamic acid, respectively (Palmer 2019; Palmer et al. 2021). G protein-coupled receptors (GPCRs) have been identified as the cognate receptors for the sweet, bitter, and umami categories of tastants (TAS1R2/R3, TAS2, and TAS1R1/R3 receptors, respectively, for each category, reviewed in Palmer 2007, 2019), and ion channel mechanisms have been elucidated that are thought responsible for the taste qualities of salty (Nomura et al. 2020; Roebber et al. 2019) and sour stimuli (Teng et al. 2019; Zhang et al. 2019, 2021). A growing body of evidence supports the distinction of a fat taste quality stimulated by long-chain fatty acids, with the scavenger receptor CD36 and the GPCR GPR120 as likely receptor candidates (Hichami et al. 2021). Recently, a taste cell mechanism has appeared to explain the sensory qualities associated with water (Zocchi et al. 2017) as a lingual stimulus (Rosen et al. 2010).

All behavioral assays (including human taste perception) of taste quality are, in one form or another, designed to measure the degree of discrimination or generalization between a sample tastant and a reference standard. At the cellular and molecular levels taste qualities are thought to arise from functionally segregated populations of cells within the taste bud that each are committed to signal one of the basic tastes (Caicedo et al. 2002; Yoshida et al. 2006). Each taste cell population selectively expresses receptors that are exclusively activated by tastants from one basic taste category. The taste cell signals resulting from receptor–tastant interaction in turn are faithfully propagated by independent sets of sensory neurons all the way to distinct locations in gustatory cortex (reviewed in Yarmolinsky et al. 2009). This "labeled line" hypothesis has predominated as the most widely accepted explanation to account for distinct taste qualities, compellingly supported by experiments in which molecular genetic techniques were used to redirect the expression of receptors for "sweet" agonists to "bitter" cells, and "bitter" agonists to "sweet" cells in mice. In a reversal of the consummatory behavior observed of wild-type mice, those genetically engineered mice avoided sucrose solutions and ingested solutions of substances considered bitter to humans (Mueller et al. 2005; Zhao et al. 2003). However, evidence contrary to a strict labeled line account of taste quality has been

present in the literature, where communication among ensembles of taste cells produces a combinatoric coding of taste signals (Roper 2021; Tomchik et al. 2007). More broadly, chemosensory discrimination apparently does not exclusively require a strict labeled line, as is evident in olfaction (Stettler and Axel 2009) and for psychoactive drugs, which act upon receptors distributed throughout the nervous system but still are behaviorally discriminated according to their stimulus properties (Porter et al. 2018).

Palatability is a term given to the preference for what is tasted, defined either as a measure of the consumption of a substance (reviewed in Palmer 2007, 2019) or, in human studies, the language subjects use to describe their preference for an ingestible substance (Wichchukit and O'Mahony 2015). Generally, palatability or preference is presented as a process that is dependent upon but distinct from taste quality. Preferences for substances taken into the oral cavity are acquired by associations between taste quality (and potentially other oro-sensory properties) and physiological consequences of ingestion. The associations are acquired through the experiential history of an individual organism (Chambers 2018; Reilly and Schachtman 2008) or are genetically determined (Diószegi et al. 2019). Measurements of palatability often are used to infer taste quality, particularly in animal experiments where the dependent variable is volume of consumption (Inoue et al. 2007; Tordoff and Bachmanov 2003) or the rate of licking from sipper tubes (Devantier et al. 2008; Long et al. 2010) or from 96-well plates (Palmer et al. 2013). In these cases the behaviors usually are referred to as "taste-guided" (Long et al. 2010; Spector 1995) to emphasize the distinction between processes exclusive to taste quality signaling and those of potentially additional physiological contributions to ingestive behaviors (Schier and Spector 2016).

The literature further distinguishes chemesthesis as a category of chemosensory responses to chemical irritants (Roper 2014; Slack 2016) that come into contact with receptors, such as transient receptor potential (TRP) channels, that are expressed in sensory nerve endings of the trigeminal nerve (Rhyu et al. 2021). The oro-sensory qualities associated with capsaicin through activation of TRPV1 (Long et al. 2010) and allyl isothiocyanate (AITC) and oleocanthal through TRPA1 (Des Gachons et al. 2011) are representative of chemesthesis.

Additional oro-sensory qualities that are thought to be due to processes separate from taste cell activity are recognized and studied, such as "astringency" (Green 1993; Schöbel et al. 2014), "mouth feel" (Simons et al. 2019), texture (Liu et al. 2017), and possibly sensory signals that result from osmotic changes (Gilbertson 2002; Lyall et al. 1999). Taste, defined as signals that result from the stimulation of taste cells, is one among many potential sources of sensory stimuli, also including olfactory (Djordjevic et al. 2004; Small and Prescott 2005), visual (Sakai et al. 2005; Spence et al. 2010; Zampini et al. 2007), auditory and verbal cues (Okamoto et al. 2008; Spence and Shankar 2010), and any other evoked cognitive associations (Liang et al. 2021; Noel and Dando 2015; Velasco et al. 2016) that contribute to the overall perceptual impression, or "flavor" (Auvray and Spence 2008; Prescott 1999), of substances taken into the oral cavity. It is important to reiterate and emphasize here that by scientific convention "taste" refers to the physiological and

perceptual phenomena that result specifically from the receptor-mediated functions of the specialized taste cells of the taste bud, distinct from other oro-sensory sensations that might be conflated into more inclusive notion of what is meant by "taste."

2.3 The Pharmacology of Taste

Certainly, any function of an organism that is affected by changes in tastant receptor activity can be, and has been, studied without reference to pharmacological principles when addressing experimental questions important to other scientific paradigms. However, the overarching goal of a pharmacological approach to the study of taste is the characterization of the relationships between tastants and all physiological consequences that follow from their effects on tastant receptors. It is the cause-and-effect association between tastant and taste response that is of interest to pharmacology. The lawfulness of that association should be reflected at every level of complexity, from the moment of signal transduction all the way to the subjective experience of the taste perception.

By the early 2000s the receptors that tastants act upon to generate the signals ultimately interpreted as sensory percepts of taste were discovered. They, generally, are the same molecular entities that had been the primary focus of the science of pharmacology since the early 1900s. Though the molecular objects underlying the phenomena under scrutiny were not known by pharmacologists until the second half of the twentieth century, the functional properties of receptors were understood and well-characterized prior to the time of their physical isolation. A set of principles emerged, coalescing into a general theory of receptor occupancy, that reliably accounts for the actions of receptors and the phenomena they control, including taste.

3 Essentials of Receptor Occupancy Theory

Careful measurement and experimental analysis of physiological changes caused by controlled administration of chemical agents to biological systems led to a concept of "receptor" that was defined not on its physical dimensions but on how it behaved (Barwich and Bschir 2017). Increasingly precise quantification of the effects of chemical agents on biological systems accumulating over the twentieth century led to formulation of principles that formed the theoretical basis of the scientific discipline of pharmacology. Certain physical properties of the previously unidentified receptor entity were deduced, and now with modern biophysical methodologies have been confirmed. The receptors have been isolated and identified as proteins (Grisshammer 2009; Lefkowitz 2013), their physical properties quantified (Hanson and Stevens 2009), and the molecular mechanisms underlying their activity determined (Rosenbaum et al. 2009).

Receptors are finite, countable objects, macromolecules that are structured such that they can accommodate a tight association with a second, usually small, molecule. The association, traditionally referred to as a "complex," is achieved by a complementarity between the ligand and a pocket in the surface of the receptor, both in terms of geometric shape and physico-chemical properties. Attractive intermolecular forces (for example, van der Waals forces, hydrogen bonds, ionic interactions) between the functional groups of the ligand and the R groups of the amino acids lining the pocket determine the duration of the receptor occupancy.

This first step describes the basics of a bimolecular reaction that is formalized with the notation of chemistry as follows:

$$L + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} LR$$

where L represents the ligand, R is the receptor, and LR is the ligand-receptor complex. The bidirectional arrows indicate a dynamic equilibrium between a forward reaction from reactants L and R to product LR, and a reverse reaction, the dissociation of the LR complex back to free L and R. Above and below the arrows are rate constants k_1 and k_2 for the forward and reverse reactions, respectively.

The rate constants are proportionality constants that relate the rate of reaction to concentrations of reactants. The rate, r, of the forward and reverse reactions are, respectively

$$r_1 = k_1[L][R] \quad (\text{forward reaction, the "on rate"}) \tag{1}$$

$$r_2 = k_2[LR] \quad (\text{reverse reaction, the "off rate"}) \tag{2}$$

At equilibrium the rate at which ligand binds receptor, the "on rate," is equal to the rate at which the ligand-receptor complex falls apart, the "off rate":

$$k_1[L][R] = k_2[LR] \tag{3}$$

Equations (1) through (3) are straightforward statements of the *law of mass action*, which posits that the rate of a chemical reaction is directly proportional to the product of the concentrations of the reactants, and further implies that the ratio of the concentrations of reactants to products will be constant at equilibrium.

From the information in Eqs. (1) through (3) a function can be derived that quantifies the fraction of a finite population of receptors that is occupied at any given concentration of ligand. The derivation, which is a series of simple algebraic manipulations (for examples, see Kenakin 2018; Limbird 2006), yields the following expression of receptor occupancy:

$$\frac{[L]}{\frac{k_2}{k_1} + [L]} = \widehat{p} \tag{4}$$

where $\widehat{p}$ is the fraction of occupied receptors at a given concentration of L. The ratio of the constant for the off rate, k_2, to that of the on rate, k_1, that appears in the denominator is also shown from the derivation to be equal to K_D, the dissociation constant, which is the concentration of L that achieves a fractional receptor occupancy of 0.5.

$$\frac{[L]}{K_D + [L]} = \widehat{p} \tag{5}$$

The K_D is the defining parameter of the affinity of a ligand for a specific receptor and is unique to each ligand-receptor pairing. The K_D also is the location parameter of the entire receptor occupancy function.

Equation (5) is formally equivalent to the Langmuir isotherm describing adsorption of gases to a surface (Langmuir 1918), and also to the Michaelis-Menten model for enzyme kinetics (Srinivasan 2021). The equation also was derived by Archibald Hill in the context of oxygen binding to hemoglobin (Hill 1910) and it is conventional to refer to the equation as the Hill-Langmuir equation in the context of receptor occupancy (Finlay et al. 2020; Neubig et al. 2003). A very similar form of this equation frequently is used as a quantitative model for analyzing concentration-response data (described below), and in that context is referred to simply as the Hill equation (Hill 1909; Neubig et al. 2003).

The equation describes a rectangular hyperbolic function. To account for cooperativity in binding the equation is modified by raising the ligand concentration variable to an exponent that reflects the slope of the function (Fig. 1). Under the conditions of a simple bimolecular association between ligand and receptor, the value for the exponent is 1, and accordingly, the slope of the function is 1. The slope exceeds a value of 1 if binding is positively cooperative – the formation of ligand-receptor complexes increases disproportionately with rising ligand concentrations.

Important characteristics of receptor behavior are immediately revealed by a plot of the Hill-Langmuir equation. When ligand concentration is plotted on a common logarithmic scale, the function is sigmoidal, a graphic presentation that enhances visual inspection of the quantitative characteristics of the ligand–receptor interaction (Fig. 1). Between, roughly, 15 and 80% of receptor occupancy, the function is practically linear. Beyond the linear portion of the curve is a region of saturation, a manifestation of the fact that progressively fewer receptors are open for ligand binding. From the function it can also be calculated that, under conditions of a simple, reversible bimolecular reaction, slope of 1, the ligand concentration required to occupy from 10 to 90% of the receptors will range by 81-fold (Figs. 1 and 2). Most of the concentration-occupancy function therefore is contained within a range of less than two $\log_{10}$ units, even less if binding is positively cooperative (Figs. 1 and 2). Functions that exceed this range imply additional complexities of ligand–receptor interactions, such as negative cooperativity, or the presence of multiple receptors in

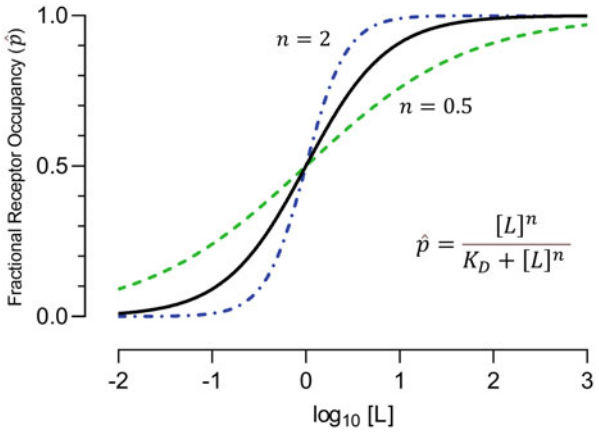

Fig. 1 Receptor occupancy function. The fraction of receptors occupied is plotted as a function of the ligand concentration ([*L*]) in common log units. In the figure, concentration in molarity is assumed and normalized to a value of 1 ($\log_{10} = 0$) for the purpose of generalizing the function to any range of concentrations. The concentration of ligand that occupies half of the total receptor population is equal to the K_D, the defining value for the affinity between ligand and receptor, and centers the domain for the function. Reversible bimolecular binding at equilibrium is assumed. Slopes greater than or less than unity, appearing in the exponent *n*, indicate cooperativity (positive or negative, respectively). The slope of the function does not impact the location of the K_D. The equation for the function defines the limits of the relationship between ligand concentration and receptor occupancy and sets the capacities for all concentration-response functions consequent to the formation of the ligand-receptor complex

the examined system that bind with differing affinities to the same ligand, all of which can be confirmed by further analysis with the right pharmacological tools and methods (if they are available; Christopoulos and Kenakin 2002).

3.1 The Concentration-Response Function and Its Relationship to Receptor Occupancy

The Hill-Langmuir equation presents a rigorous quantitation for the fraction of receptors that will be occupied at any given concentration of ligand, and is thus the centerpiece of the conceptual framework for all else that follows in the study of receptor-mediated functional biology. The general restrictions explicit in the concentration-occupancy function also are reflected in the *concentration-response* function. The ligand and receptor of interest here, of course, are a tastant agonist molecule and its cognate receptor. Since most of the concentration-occupancy function is contained within a range of less than two $\log_{10}$ units, the tastant concentration-response function that results from receptor occupancy also should be similarly restricted (Fig. 2). Functions that exceed these limits imply possible contributions of additionally activated tastant receptors, or perhaps other activities

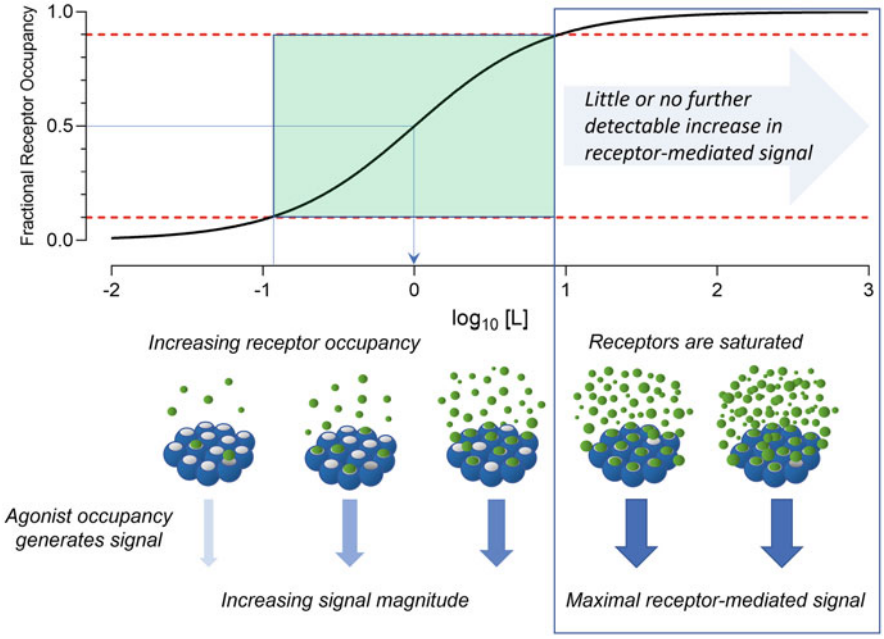

Fig. 2 The limits of receptor occupancy and implications for receptor signaling. Fractional receptor occupancy is plotted as a function of the concentration of ligand, here assumed to be an agonist. The function is defined by the Hill-Langmuir equation and assumes a slope of 1. Below the graph are drawings depicting receptors (blue ovals) increasingly occupied by agonist (green spheres) as agonist concentrations rise. Unoccupied receptors are indicated by a gray oval, representing open binding pockets, at the top of each receptor. The receptors are drawn to approximate correspondence with the portion of the occupancy curve above them. Signals that result from agonist occupancy accordingly increase in magnitude as agonist molecules occupy more and more receptors. The response capacity is maximized at saturation, beyond which no further increases in signaling or consequent response is possible through this receptor population. The dashed horizontal lines indicate fractional occupancy at 0.1 and 0.9. From the function it can be seen that most of the biological activity related to this receptor population occurs within an 81-fold range (<2 log units) of agonist concentration

unrelated to receptors that impact the dependent variable measured in any assay of taste.

Equation (5) also was derived by Alfred Joseph Clark (Clark 1927) as an attempt to generalize receptor occupancy to the magnitude of effect caused by any agonist. Later, Lloyd Beidler derived the same equation to quantitatively characterize concentration-dependence of gustatory nerve responses to tastants applied to rat tongue (Beidler 1954). Both Clark and Beidler assumed that the fraction of receptors occupied by agonist would be linearly related to the fraction of the maximum response. The additional property of efficacy (Stephenson 1956) was conceived to account for the observation that some agonists appeared to cause maximal effects while occupying a relatively small percentage of receptors, whereas other agonists never achieved maximal effect even at concentrations expected to saturate the

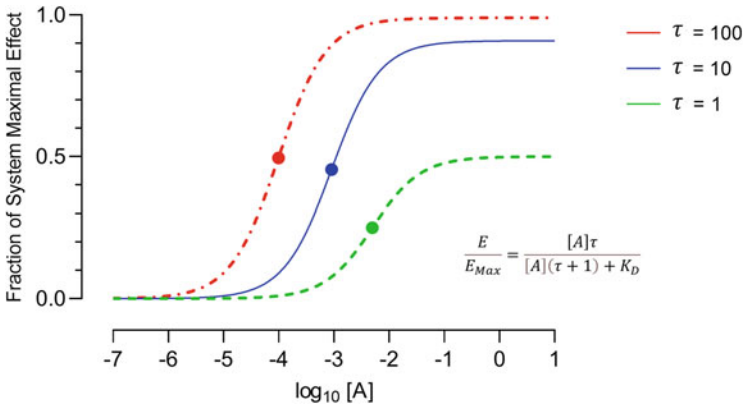

Fig. 3 The concentration-response function by the operational model of agonism. The curves in the figure are fit by the operational model of Black and Leff (1983), with a slope of 1 assumed, and the value of τ varied as shown. The y axis indicates the maximal range of capacity for change within the biological system under experimental scrutiny, and the x axis is arbitrary common log units of agonist concentration. The system could be a simple smooth muscle preparation or the response capacity of the population of cells in the tongue committed to sweet-taste signaling. The ability of agonist-receptor complexes to access system capacity is a function of receptor density and agonist intrinsic efficacy, both captured in the value of τ. The green curve shows a concentration-response function that results from relatively low access to system capacity by the agonist-receptor complexes, either because overall receptor density is below capacity, or the agonist-receptor complexes do not efficiently couple to the biological system. With a τ value of 1, the receptor-complexes can achieve a maximum of half of the system's capacity for change. Increases in receptor expression or agonist intrinsic efficacy move the effectiveness of agonist-receptor complexes progressively toward system capacity, as indicated by the blue and red curves (τ of 10 and 100, respectively). The closed circles at the inflection point of each curve indicate the position of the *EC*50 on the x axis below. For the green curve, the *EC*50 should closely approximate the agonist's affinity for its receptor

receptor pool. The term *intrinsic* efficacy refers to the ability of an agonist to "activate" a receptor (Clarke and Bond 1998; Kenakin 1985). High intrinsic efficacy agonists, relative to other agonists, require fewer receptors to cause changes in a biological system. In contrast, a low efficacy agonist, or partial agonist, fails to cause maximal effect even at saturating concentrations (Fig. 3). Evidence of partial agonism by tastants has been obtained from cell-based assays of murine TAS2R receptors (Lossow et al. 2016), but little or none has been reported for in vivo assays of taste, to date.

3.1.1 The Operational Model of Agonism

Manifestation of agonist intrinsic efficacy can be impacted by the numbers of receptors expressed in a given biological system. A maximal effect could result from a partial agonist if levels of receptor expression are sufficiently high. Thus, the magnitude of effect caused by an agonist is determined by properties intrinsic to the agonist as well as the tissue. Both factors also determine the location of the

concentration-response function – high expression and high intrinsic efficacy tend to shift concentration-response functions to the left (i.e., lower ranges of concentration).

A quantitative model of agonist activity that links receptor occupancy, intrinsic efficacy, and receptor density to the concentration-response function was derived by Black and Leff (1983) and Black et al. (1985). Essentially treating the agonist-receptor complex, *AR*, as the stimulus that launches the signal transduction chain of events, and from the former assumption of a direct correspondence between fractional receptor occupancy and physiological effect, Eq. (5) is reframed in the operational model as

$$\frac{E}{E_{\text{Max}}} = \frac{[AR]}{K_E + [AR]} \tag{6}$$

where E_{Max} is the maximal effect possible in the receptor-linked system, and K_E is the concentration of agonist-receptor complex, $[AR]$, that causes half-maximal effect. The operational model further introduces a "transducer ratio," $\boldsymbol{\tau}$, a measure of the efficiency of the transduction of signal from the agonist-receptor complex:

$$\tau = \frac{[R_T]}{K_E} \tag{7}$$

Here, the term $[R_T]$ represents the total population of receptors available to the agonist. Black and Leff (1983) incorporated these concepts into a step-by-step derivation that begins with Eq. (5) to arrive at the following relationship:

$$E = \frac{E_{\text{Max}}\tau[A]}{(K_D + [A]) + \tau[A]} \tag{8}$$

The equation emphasizes the impact of intrinsic efficacy and receptor density on the translation of receptor occupancy to a concentration-response function. Both the maximal response magnitude and the $EC50$ for an agonist are impacted by τ (Fig. 3).

The logistic form of the operational model is given by the equation:

$$E = \frac{E_{\text{Max}}[AR]^n}{K_E + [AR]^n} \tag{9}$$

which includes exponents to account for slopes differing from unity. In most practical applications, the Hill equation (or a closely related logistic version which allows determination of values for asymptotes) is used (Neubig et al. 2003):

$$\frac{E}{E_{\text{Max}}} = \frac{[A]^n}{[EC_{50}]^n + [A]^n} \tag{10}$$

Here, the exponent n is referred to as the Hill coefficient, again reflecting the slope of the concentration-response function. The main difference between Eqs. (9)

and (10) is that the former conceptualizes the agonist-receptor complex as the unit of stimulus, whereas the latter equation frames the concentration-response function in terms of the agonist, the independent variable that is under direct control of the investigator.

4 Conclusions to be Drawn from Receptor Theory: What Is to be Expected of Taste?

The equations detailed above provide a well-reasoned progression from the chemical event of receptor binding to its consequent physiological effect. The theory quantitatively traverses the interface of chemistry and biology, and by doing so defines the agonist concentration-dependence of any physiological action that is linked to receptors. Scientific theories are best when they set clear limitations to what is possible for the natural phenomena they purport to explain. Taste is universally acknowledged to be mediated by receptors, and so also should operate within the bounds set by receptor theory.

The relationship between tastant concentration and magnitude of taste response should assume a hyperbolic (or related logistic) function. Most of the function should be contained within a span of approximately two $\log_{10}$ units. There must be an upper limit to the concentration-dependence of tastant responses as the population of tastant receptors saturate with tastant. Additional increases in tastant concentration beyond that limit should not result in any further measurable increase in taste (Fig. 2). One potential nuance to this rule is that higher concentrations could result in a faster onset of action (by the forward rate of the ligand binding reaction, r_1, defined above), which could be a detectable cue incorporated into the taste response. However, rate of onset also will soon reach a limit to its potential as a discriminable cue.

The location of the concentration-response function, indicated by the $EC50$ parameter, is determined by the agonist's affinity for its receptor (K_D) and factors controlling receptor density and coupling efficiency (factors represented by τ, Fig. 3). Potentially, then, genetic variations that impact tastant receptor structure in the binding site, in the domains that couple the receptor to signaling, or in the promoters for receptor (or G protein) expression, could shift the concentration-response functions for taste to lower or higher ranges across individuals. Threshold measurements for taste, a common focus of psychophysical studies, would be affected by shifts in tastant potency. However, differences among individuals in thresholds for taste also could be due to other physiological processes that are not directly related to the functionality of tastant receptors. Especially where inter-subject differences in thresholds are small, analysis of the entire concentration-response relationship would bolster correlations of taste-sensitivity phenotypes with specific genetic variants of tastant receptors.

Efficiency of coupling also is partly determined by the agonist, and it is possible that some tastants are more effective than others in translating receptor occupancy into receptor signaling (the property of intrinsic efficacy). In vivo demonstration of a

low efficacy tastant agonist would, by itself, be an important discovery; but a partial tastant agonist would be particularly useful for identifying receptor density as a determinant of taste-sensitivity phenotype.

The above equations and reasoning rest upon an assumption of equilibrium conditions. A question then naturally arises over whether receptor occupancy theory is directly applicable to taste, which is a rapid response occurring within milliseconds of contact with a tastant agonist (Stapleton et al. 2006). As of yet, molecular assays capable of directly determining the kinetics of tastant receptor occupancy are not available. However, there should be a correspondence between response magnitude and a specific fraction of occupied receptors, even if tastant binding equilibrium has not been reached within the timeframe of a taste response.

Concentration-response analysis of data from cell-based assays of heterologously expressed tastant receptors provides an appropriate test of the predictions of receptor theory on transient responses that are likely to occur under hemi-equilibrium conditions (Charlton and Vauquelin 2010; Kenakin et al. 2006).

4.1 Characteristics of the Concentration-Response Functions from Cell-Based Assays of Recombinant Tastant Receptors

Cell-based assays of heterologously expressed TAS2R (Meyerhof et al. 2009), TAS1R2/R3 (Li and Servant 2008; Servant et al. 2010), and TAS1R1/R3 (Servant and Frerot 2021) receptors have been in use for over two decades, both for basic research and for commercial purposes. The assays record tastant-stimulated mobilization of intracellular calcium through the use of fluorescent dyes and imaging devices such as FLIPR (Woszczek et al. 2021). Calcium responses occur within seconds of addition of tastant, and in that regard cell-based assays serve as a suitable model system for pharmacological comparison with similarly rapid in vivo tastant responses.

The characteristics of the concentration-response functions obtained from recombinant tastant cell-based assays are quite consistent with the operational model and receptor occupancy theory upon which it is based. An abundance of data is available from human TAS1R2/R3 assays of concentration-dependent responses to sucrose and other sweet tastants to serve as a useful illustration. Concentration-response functions for sucrose (Li et al. 2002; Servant et al. 2010; Xu et al. 2004; Zhang et al. 2010) are anchored at the low end by concentrations of approximately 3 to 10 mM, after which the functions rapidly accelerate through a phase that is essentially linear. The midpoint of the linear portion, the *EC*50 value representing sucrose potency, is explicitly stated in some papers with values of 62, 52 (Servant et al. 2010), and 19.4 mM (Xu et al. 2004), and where not explicitly stated can be seen from inspection of graphs to range between approximately 30 and 60 mM (Li et al. 2002; Xu et al. 2004; Zhang et al. 2010; summarized in Table 1 of Palmer 2019). The curves also can be seen to approach an asymptote as concentrations reach or exceed 100 mM, where no further increases in responsiveness occur. Thus, the entire concentration-response functions for sucrose obtained from cell-based assays for

recombinantly expressed TAS1R2/R3 are contained within approximately 1.5 to no greater than two $\log_{10}$ molar units of concentration range. The steepness of the curves plausibly is explained by the hemi-equilibrium kinetics of receptor occupancy expected of calcium signaling assays (Charlton and Vauquelin 2010). Similar characteristics for concentration-response functions for the TAS1R2/R3 agonist sucralose in cell-based assays also are evident, but shifted approximately 1,000-fold to the left of that for sucrose; the median of multiple *EC*50 determinations by Servant et al. (2010) was 61 μM, and their functions saturated as concentration approached 1 mM.

4.2 Concentration-Dependence of Human Taste

4.2.1 Power Functions for Taste Intensity

Concentration-dependent measure of suprathreshold tastant responses has been conducted for many decades through the use of scales of taste "intensity." Historically, most of the development of scales for rating sensory intensity developed out of experiments involving manipulation of the energy output of visual or auditory stimuli (Stevens 1957), but eventually scales of taste intensity also were designed (Stevens 1969). For taste intensity, subjects are instructed to report the magnitude of their resulting sensory experience in terms of numbers, as in scales of magnitude estimate (Stevens 1969), or verbal labels which have been equated with a numeric scale, as in the labeled magnitude scale (LMS; Schifferstein 2012) and generalized (or general) labeled magnitude scale (gLMS; Bartoshuk et al. 2004).

Taste intensity rating scales are considered to remedy both logistical and conceptual limitations of threshold measurements, which focus only on the lowest detectable concentrations of tastant. Statistical resolution of thresholds requires many trials of samples containing tastant and "blanks" (vehicle alone), and the results do not necessarily inform on responsiveness to suprathreshold concentrations that normally are encountered by humans as they sample sources of tastant from their environment (Keast and Roper 2007). Concentration-dependence of taste intensity is described as progressing from thresholds of detection through increases in magnitude to a hypothetical asymptote, where further increases in tastant concentration of tastant no longer cause increases in perceived taste intensity (Low et al. 2014). Nominally this description would be consistent with the predictions of receptor occupancy. However, empirical results from studies of the relationship between taste intensity and tastant concentration often do not agree with this description; in particular, taste intensity frequently has been shown to continue increasing without saturation as tastant concentration rises. The range of taste-active concentrations also appears to exceed the theoretical limits predicted by receptor theory.

From the earliest studies of suprathreshold taste intensity measurements, the resulting concentration-intensity relationships were fit to a power function. Such results were viewed as an expected generalization of the model promoted by Stanley S. Stevens (Stevens 1957), which purported that the relationship between the intensity of a physical stimulus and the perceived magnitude of sensation is best fit

by a power function for all sensory modalities. The function is described by the equation:

$$\psi = kS^n$$

where ψ is the subjective sensation experienced, S is the stimulus (in the context of taste, the variable represents tastant concentration), k is a constant, and n is the empirically determined exponent for the power function that fits the data.

A defining characteristic of power functions is that they can be linearized by a log transformation as follows:

$$\log \psi = n \log S + \log k$$

A plot of the function on a log-log scale produces a straight line with a slope defined by the power exponent, n.

Stevens applied the power function model to data obtained from subjects who were instructed to assign numbers to the magnitude of sensation they experienced across a range of sucrose concentrations (Stevens 1969). The results of Steven's experiment are shown in Fig. 4 (redrawn from the original publication). The slope of the plot yields a power of 1.3 for the function. A power function with an exponent >1 quantitatively describes an accelerating function (it does not saturate).

Steven's results, which he reported to have replicated in additional experiments, are not explained by receptor theory. Receptor occupancy must saturate, and therefore any response that is functionally related to receptors also must saturate. Stevens acknowledged that eventually a saturation might be expected as the capacity of the nervous system for processing incoming sensory information was approached, but it is the saturation of receptor occupancy that matters in setting the limits to generating any signals that result from tastant agonist activity.

Not all investigators have reported an exponent of 1.3 from the power function obtained for sweetness intensity rating of sucrose. A paper by Meiselman (Meiselman 1971) addressing questions over the potential effects of tastant presentation procedure (sip, anterior dorsal mouth flow, whole mouth flow) on taste intensity functions summarized in a table the exponents of power functions from taste intensity studies of NaCl, quinine, sucrose, saccharin, HCl, and citric acid. A wide range of exponent values, above and below 1, for all tastants is evident. The table suggests a tendency for stimulus presentation by flow methods to result in lower power function exponents in comparison to sip methods. However, exponents obtained from each of the methods separately considered also vary widely. For example, sip methods from 11 studies of sucrose taste intensity produced power functions with exponents that range from 1.8 to 0.62. More recently reported values for sucrose sweet taste intensity continue to range below and above 1 (for example, values of 0.78 from Green et al. (1993), and 1.3 from Wee et al. (2018)).

There are different versions of scales and methods of their use, and there have been continuous debates over the merits and shortcomings of each (Schifferstein 2012). It often has been argued that the scale design and attendant methods of its

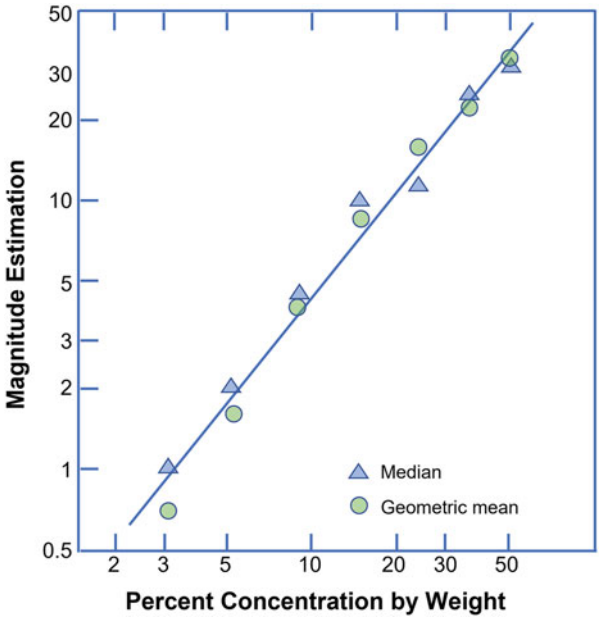

Fig. 4 Sweet taste intensity magnitude estimation. The figure is redrawn from Fig. 2 of Stevens (1969). The figure shows a log-log plot of the magnitude of subjectively experienced taste intensity experienced (y axis) from varying concentrations of sucrose solutions (expressed as percent W/W on the x axis, ranging from 3% (87 mM) to 50% (1,450 mM)). Subjective intensity was estimated by each subject using a scale for magnitude estimates. Prior to testing the scale was calibrated by establishing a standard of sweet taste intensity. The standard was created by giving each subject a single concentration of sucrose to taste and instructing them that the intensity experienced should be a predetermined value (10, for example). Subjects were then further instructed to assign numbers expressed as ratios of intensity relative to the standard for all subsequently presented sucrose concentrations. Instructions included detailed explanation of how to assign ratios. The data were fit by a power function with an exponent of 1.3 (the slope of the line in the log-log plot), indicating continuous acceleration of the function over the range of sucrose concentrations tested. In some instances, subjects did not report their sensory magnitude estimates as ratios, and such cases suggested to Stevens a failure of the subject to "grasp the concept of proportionality"

administration could bias the experimental outcome (Lawless et al. 2000; Meiselman 1971; Running and Hayes 2017). However, there is no accounting for such wide shifts from negative to positive in the exponents of power functions fit to the various datasets, nor even why a concentration-response function for receptor-governed responses should be fit by a power function (particularly non-saturating power functions) instead of a hyperbolic function. In a recent report (Wee et al. 2018) of a concentration-response analysis performed on 16 different sweeteners, sweetness intensity rating data were fit both to a power function model and also to the Hill equation. The sweetness intensity rating data for sucrose fit by a power function returned an exponent of 1.3 indicating positive acceleration throughout. Curiously, the same dataset analyzed by the Hill equation yielded saturating functions. The Hill

analysis of sucrose taste intensity by Wee et al. is consistent with the results reported by Antenucci and Hayes (2015), a similar analysis performed on sucrose intensity ratings from a group of 401 subjects. In stark contrast, the results of the power function analysis of sucrose taste intensity by Wee et al. are inconsistent with the Hill analysis of Antenucci and Hayes (2015) and also with their own Hill analysis.

Ultimately there is no theoretical basis for a power function model to quantitatively describe tastant–agonist interactions. There is no need, therefore, to rely on them for analyzing taste intensity data. Concentration-intensity relationships for tastants have been graphically represented and statistically treated without power function curve fits (or any other model, for that matter), and by doing so achieve experimental objectives without wading into the difficulties of interpretating the curve fits outlined above. For example, the concentration-intensity relationship for sucrose using the gLMS, plotted as a simple point-to-point graph, demonstrated the perceptual effect of antagonizing the TAS1R2/R3 receptor with clofibrate (Kochem and Breslin 2017).

4.2.2 The Relationship of Taste Intensity to Taste Thresholds

There is, however, another question that arises from the results of many taste intensity experiments regardless of curve fitting models. Relative to measurements of taste detection thresholds, taste intensity ratings often occur across concentrations that range greater than would be expected for a receptor-mediated phenomenon. The range of taste-active concentrations should be anchored at the low end by thresholds. Most threshold measurements are achieved by presenting two or more samples to the subject in a randomized or stepwise pattern, one with a "blank" (usually water) and the others with tastant solution. The lowest concentration of tastant that is statistically determined to be correctly distinguished from water represents the threshold.

Despite the likely impact of a variety of conditions and subject-dependent variables on taste sensitivity (Trius-Soler et al. 2020), the values obtained for sucrose detection generally range around 5 to 10 mM (reviewed in Palmer 2019, and Trius-Soler et al. 2020). For example, average sucrose thresholds of 6.8 and 10.83 mM in healthy adults have been reported by Petty et al. (2020) and Zhang et al. (2008), respectively. A recent application of signal detection analysis to generate *d'* values (a measure of discriminability) from a method of constant stimuli experiment (Palmer et al. 2021) indicated that, on average, adults could discriminate 5 mM sucrose from water. Collectively, these results strongly suggest that concentrations of sucrose near 5 to 10 mM also should anchor the low end of the concentration-response function for sucrose taste.

In contrast, sweetness intensity ratings of sucrose typically begin to register at higher concentrations, apparent in Steven's data (see Fig. 3) extrapolated to a low concentration of approximately 2% w/w, or 58 mM, and also in those of Kochem and Breslin (2017) mentioned above. In the latter study, sweetness intensity ratings were anchored for sucrose (in the "neat," or without antagonist, condition) at the lowest concentration tested, 30 mM, where the numeric value for intensity would be equivalent to a label of "barely detectable" by the gLMS (Bartoshuk et al. 2004). In both studies, sweetness intensity continued to rise with sucrose concentration up to

the highest concentration tested of approximately 1,500 mM, at which point saturation was not evident. Increasing taste intensity as sucrose concentrations exceed 1 M is reported in many studies (reviewed in Palmer 2019). Recently, sucrose intensity ratings obtained by the gLMS in a group of type 2 diabetics were shown to continue increasing at 2.02 M (Vidanage et al. 2022).

Possibly the conundrum of ratings that translate to "barely detectable" in taste intensity scales for sucrose concentrations that are readily detectable in threshold procedures is explained by contrast effects, a suppression of taste intensity perception when judging low tastant concentrations in a test which includes trials of substantially greater concentrations (Lawless et al. 2000; Shepard et al. 2017). More importantly, however, the range of taste-active concentrations spanning from threshold detection through those of taste intensity measures exceeds the range set by the limits of receptor capacity. In the case of sucrose, there is a 300-fold range of taste-active concentrations, from approximately 5 at threshold to 1,500 mM, with no indication of response saturation in most studies. The problem is even more pronounced with sucralose; the span of taste-active concentrations appears to begin with thresholds of 11.9 uM (Breslin et al. 2021) but sucralose sweetness intensity ratings continue to increase at 100 mM (Kochem and Breslin 2017), or a 10,000-fold range of concentrations. Data generated by sweetness intensity measurement are difficult to reconcile with the predictions of receptor theory. Perhaps something more than TAS1R2/R3 receptor function is involved in the perception of sweet taste intensity. If taste is defined by taste receptor signaling, which is determined by tastant receptors, then taste intensity is a more comprehensive oro-sensory experience.

4.3 Dependent Variables in Human Taste Measurement

There is no doubt that a causal relationship exists between tastant concentration and measures obtained by taste intensity scales – as concentration increases, subject ratings of taste intensity predictably increase. However, the issues raised here over the range of concentration-dependence and the quantitative characteristics of the functional relationship suggest a fundamental question over what, precisely, defines "taste intensity" as a dependent variable to be measured. The nature of sensations – what they are and how they represent the external world to the subject – has a long history of philosophical discourse that is central to Western thought. Here, however, the focus will remain limited to the practical aspects of defining taste as a dependent variable for measurement and how the resulting data are to be interpreted.

A different approach to measuring human taste as a function of concentration recently was reported (Palmer et al. 2021) that was based on a taste discrimination procedure. In contrast to most discrimination experiments, where the focus is on threshold determination, the procedure of Palmer et al. (2021) trained subjects through an automated game-like operant task to compare a range of sucrose concentrations (from 3.9 to 500 mM, randomly presented) to two standards, water and 200 mM sucrose. The solutions were self-administered to the tongue in aliquots of 200 μl from an electronic pipette. The datum was a binary "sucrose-like" or

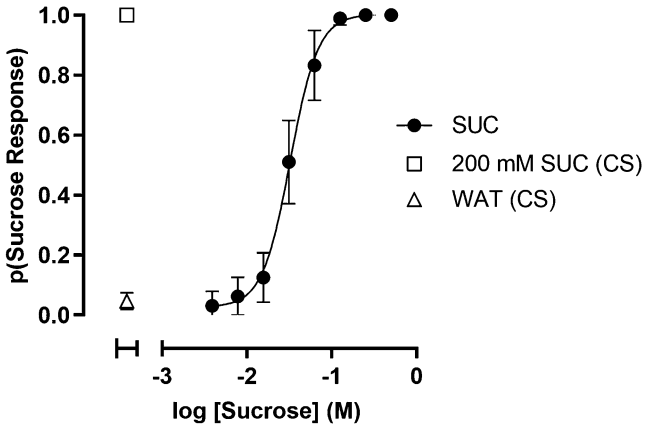

Fig. 5 Concentration-response function for sucrose taste discrimination. The figure is from Palmer et al. (2021), its use here is permitted through the Creative Commons License. A cohort of 8 subjects was trained through a game-like interactive algorithm to associate coordinates on a touch-sensitive laptop display with two standards (control stimuli, CS), water (WAT) and 200 mM sucrose (SUC), automatically drawn in 200 μl aliquots from a 96-well plate and self-administered to the tongue. Each of the 96 trials in a session was occasioned by a consequence – a virtual poker chip appeared on the display that represented actual monetary value if the correct target was touched, or a reduction of value if an incorrect choice was made. Once a criterion of test-readiness (90% correct out of 96 trials) was achieved, subjects were tested with a 96-well plate containing multiple replicates of the standards and of 8 sucrose concentrations ranging in two-fold dilutions from 500 mM to 3.9 mM. All responses, regardless of target, resulted in a poker chip reward on trials from the sucrose concentration range, but only correct responses on standard trials were rewarded (errors were penalized). The resulting data set was analyzed by nonlinear regression using a logistic model based on the Hill equation. An *EC*50 of 33 mM was returned from the curve fit, remarkably similar to values reported for recombinant TAS1R2/R3 cell-based concentration-response analyses of sucrose. The function saturates between 125 and 500 mM, and the entire range of taste-active sucrose concentration spans <1.5 log units of molarity. The results are consistent with receptor theory

"water-like" choice recorded by touches to a "sucrose" target and a "water" target on a touch-sensitive laptop display. The resulting dataset, averaged across 8 subjects, was fit by a logistic equation based on the Hill equation and related operational model of agonism. The concentration-response function plotted as proportion of sucrose-like responses, shown in Fig. 5, is anchored at the low end by a minimum of responses made on the "sucrose" target (i.e., most of the responses occurred on the "water" target). The frequency of sucrose target responses increases rapidly with rising sucrose concentrations approaching a limit of essentially 100% between 125 and 500 mM.

The steep slope of the curve (Hill coefficient of 2.64) indicates a cooperative effect on the relationship between tastant concentration and taste response, with the majority of the curve contained well within a span of <1.5 $\log_{10}$ units. Saturation is readily apparent from the sigmoidal shape of the semi-log plot. The quantitative characteristics of the sucrose taste discrimination curve are completely consistent

with the function obtained from a receptor-mediated process as predicted by theory. Though the subjects in this experiment initially were trained to discriminate between 200 mM sucrose and water, perhaps regarded as a qualitative categorization, the results from this experiment clearly indicate that their discriminations also were based on concentration – an operation on magnitudes.

Ostensibly, measurement of taste intensity also must entail a discrimination between two concentrations of tastant; a discrimination process must occur or there would be no report of a difference in intensity magnitudes. Taste intensity measures are subjective measures, meaning that they are a kind of operation performed to quantify an event which necessarily can be witnessed by only a single observer – the subject who experiences the sensation produced by the tastant (Tourinho 2006). It is the subject who performs the measurement and reports the result back to the investigator. The investigator might provide examples of stimuli and how they might be rated to "calibrate" the subject (Olabi and Lawless 2008), but the dimensions of the sensory experience still are defined in the private "privileged access" (Heil 1988) of the subjective world. The subject defines the limits of what is to be considered a sensation and the dimensions of its magnitude.

Given the task of estimating the magnitude of a taste sensation, the subject is free to use any and all information available from the sensory input that obtains from oral contact with a substance. Rate of receptor occupancy is concentration-dependent (by Eq. (2)), and likely to contribute to concentration-dependence of onset of taste stimulus (Garrido et al. 2001; Yamamoto et al. 1985; Yamamoto and Kawamura 1981). The on-rate potentially could serve as the basis for discriminating between concentrations beyond those required for occupancy saturation; but on-rate also soon would reach a limit and consequently have little or no further impact on perceived intensity at much higher tastant concentrations. Clearance of tastant from the oral cavity (Luke et al. 1999; Sreebny et al. 1985) and by implication, the receptor compartment, also would be expected to be concentration- and time-dependent; potentially a discriminable cue. Furthermore, the physical properties of a tastant can change substantially as concentrations increase. A pertinent example is sucrose, the viscosity of which increases by more than ten-fold across concentrations ranging from 10 to 50% (292 to 1,462 mM; Telis et al. 2007). Chemical and physical properties of a tastant at high concentrations quite possibly could be detected by other sensory mechanisms unrelated to tastant receptors to enhance the perception of a taste stimulus already present at its maximum. These additional sources of sensory information suggested here are only conjecture, but whether they can shape the subject's estimation of magnitude is an experimentally approachable question. However, these are not pharmacological questions, which are limited to the analysis of taste defined as output of taste cell activity under the control of tastant receptors.

5 Concluding Remarks

The idea that taste is pharmacology, though perhaps currently a minority view, is not a new one. Decades ago the behavioral pharmacologist Robert Balster (Balster 1988) observed the similarities between psychoactive drugs, which generate "interoceptive" discriminative stimuli, and the exteroceptive stimulus properties of odorants and tastants:

> . . .it should be remembered that drugs are chemicals. Detection of drug stimuli could be viewed as a type of chemoreception. There are important similarities in receptor theory for drug action and current theories of olfactory and gustatory stimulus transduction.

Balster further lamented a lack of cross-fertilization between the fields of chemoreception and pharmacology. Missing at the time was a clear understanding of the molecular mechanisms of chemoreception signal transduction. Now that the molecular mediators of taste and olfaction have been identified as GPCRs and ion channels, the link to pharmacology is obvious.

A pharmacological approach to the study of taste however must remain limited to the operations of tastant receptors and those processes that are under their control. Until the ambiguities of taste intensity measurements and their relationship to taste receptor activation are resolved, their application to elucidation of receptor functionality must be accepted cautiously. For the time being, taste discrimination appears to be more in line with receptor pharmacology, and therefore might be a better choice of assay for establishing relationships between taste phenotypes to variants of receptor structure that determine receptor density and tastant affinity. This would in turn help to distinguish tastant sensitivities that are due to receptor function from those that result from physiological factors.

Pharmacological analysis of taste discrimination might further help to refine some concepts traditional to psychophysics, such as "taste intensity." In vivo demonstration of a partial agonist for taste responses would be most useful in this regard. No matter how high the concentration, the maximal effect of a partial agonist should be perceived to produce the same intensity as a submaximal concentration of a tastant of higher intrinsic efficacy. A partial agonist also should mitigate the taste intensity of a high efficacy tastant in a binary mixture if the two share the same receptor binding site. Antagonism by a partial agonist should be pronounced under conditions that promote taste receptor desensitization, as has been demonstrated for the human P2Y1 receptor low efficacy agonist ATP in a cell-based transient calcium mobilization assay (Palmer et al. 1998). Desensitization of sweet taste intensity ratings following prolonged exposure to agonists of sweeteners has been reported (Schiffman et al. 1994), presumably a consequence of time- and concentration-dependent tachyphylaxis of agonist occupied receptors.

For those who still require a medicinal application for inclusion under the purview of pharmacology, there is ample occasion for the study of taste to meet such a demand. Taste long has been associated with palatability of foods and beverages and dietary choices (Costanzo et al. 2021; Kourouniotis et al. 2016;

Yeomans 1998) and would seem an obvious driver of overconsumption. Despite years of very active research, the connection between taste and obesity still is not clear (Ribeiro and Oliveira-Maia 2021). On the other hand, loss of taste, due to damage and disease (Dawson et al. 2020; Heckmann et al. 2005; Ibekwe et al. 2020; Nakanishi et al. 2019), chemotherapy and medication (Kan et al. 2021; Kumari et al. 2017; Rademacher et al. 2020), and aging (Kaneda et al. 2000; Schiffman and Graham 2000) has clear negative impact on food intake (Risso et al. 2020), emotion (Dudine et al. 2021), and quality of life (Jeon et al. 2021; Kaizu et al. 2021). Taste also is an important factor in the adherence of orally administered therapeutic regimens, particularly among pediatric patients (Baguley et al. 2012; Walsh et al. 2014). Better understanding of the interactions between active pharmaceutical ingredients and tastant receptors that mediate aversive tastes should help toward improving the acceptability of oral formulations. There are important unmet medical needs involving taste that can be addressed through the application of pharmacological principles, as has been done for many other health-related conditions.

Taste is a unique system for in vivo pharmacologic analysis. In contrast to the pharmacology of systemically administered drugs, the impact of pharmacokinetics on tastant responses is greatly diminished. The receptors are expressed on the apical microvilli of taste cells, localized to the surface of the tongue where they are exposed to administered tastant agonists with no obvious barrier to access. The link between pharmacodynamics at the receptor compartment and the behavioral outcome should be quite direct. Taste responses are rapid and relatively easy to record, and data can be generated quickly and at low risk to subjects. Taste presents an ideal experimental system for exploring the concepts central to the paradigm of pharmacology, further suggesting a broadening of the scope of pharmacology to other types of chemoreceptor systems such as olfaction.

Acknowledgements Dr. Palmer is cofounder of and a shareholder in Opertech Bio., Inc. Some of the technology described in Sect. 4.3 (Fig. 5) is used for commercial purposes by Opertech Bio., Inc.

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