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Use of the Herb *Gymnema sylvestre* to Illustrate the Principles of Gustatory Sensation: An Undergraduate Neuroscience Laboratory Exercise

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The Indian herb *Gymnema sylvestre* has been used in traditional Ayurvedic medicine for 2000 years, most recently for the treatment of diabetes. Loose leaf *Gymnema sylvestre* can be prepared as a tea and will impair the ability to taste sugar by blocking sweet receptors on the tongue. This report describes a laboratory exercise easily applied to an undergraduate neuroscience course that can be used to illustrate the principles of gustatory sensation. Combined with a preceding lecture on the primary taste sensations, students experience and appreciate how the primary tastes are combined to produce overall taste. In addition, the exercises outlined here expand upon previously published demonstrations employing *Gymnema sylvestre* to include illustrations of the different sensory transduction mechanisms associated

with each of the four or five primary taste modalities. Students compare their qualitative primary taste experiences to salt, sugar, aspartame, chocolate, and sweet-sour candy prior to and following exposure to *Gymnema sylvestre*. The herb's impairment of sweet sensation is profound and dramatically alters the perception of sweetness in sugar, chocolate, and candy without altering the perception of the other primary tastes. The exercise has an indelible effect on students because the herb's intense effect compels students to rely on their unique personal experiences to highlight the principles of gustatory sensation.

Key words: gustation, sensory transduction, taste, tongue

There is a common misconception among the general public, including introductory level neuroscience students, that the tongue can be divided into distinct regions that are responsible for the detection of the four primary tastes. This outdated "tongue map" on which the taste of sweet is limited to the tip, sour and salt to the sides, and bitter to the back of the tongue is based on an incorrect translation of nineteenth century German research (Smith and Margolskee, 2001). Over the past several decades, gustation researchers have demonstrated that all areas of the tongue are responsive to each of the primary tastes. Two competing yet complimentary theories govern the current conception of the neural code for taste. The "labeled-line" theory postulates that distinct cell types respond best to one of the primary tastes and form distinct channels or "labeled-lines" that represent salty, sweet, sour, and bitter. The "across fiber pattern" theory suggests that our perception of taste is represented by the pattern of activity of many multisensory taste afferents (Erickson, 1982; reviewed in Schiffman, 2000; and Smith et al., 2000). Perhaps the best explanation of the perception of taste quality draws from each theory. Taste cells, instead of being exclusively sensitive to one taste may have a distinct multisensory taste profile that responds best on one taste. Similarly, integration of taste information likely occurs in the taste bud as well and it is possible that taste quality is represented by the collective taste profiles or patterns of activity of many taste afferent neurons.

An explosion of taste research in the past decade has revealed a variety of receptors and signal transduction pathways involved in taste sensation. Sodium chloride elicits the sensation of salt when Na⁺ ions flow through amiloride sensitive Na⁺ channels, ultimately resulting in

taste cell depolarization. Sour sensations are initiated by protons in acidic substances which gate a cation conductance in an acid sensing ion channel (ASIC) or in some cases, block the flow of K⁺ ions in apical K⁺ channels. Sweet tastes are mediated primarily by adenylyl cyclase and phospholipase C activated by sweet molecules binding to G-protein coupled receptors (GPCRs). Bitter compounds bind to GPCRs which activate the G-protein gustducin leading to the activation of a phosphodiesterase and PLC. Finally, umami the fifth primary taste, has been associated with monosodium glutamate activation of metabotropic glutamate (mGlu4) receptors or other amino acid sensitive receptors. The end result of activation of most taste receptors is a depolarization of the taste cell resulting in voltage gated Ca²⁺ channel activation and release of neurotransmitter at the basal cell surface. For reviews see Gilbertson et al., 2000; Lindemann, 2001; Gilbertson and Boughtner, 2003. It is thought that the primary tastes are associated with general types of nutritive or potentially toxic substances. For example, the taste of sweet signals high calorie sugar-containing foods, umami signals protein-rich foods, and bitter signals potentially toxic or poisonous substances.

The concepts of taste sensation and perception and the contributions of the labeled line and across fiber pattern theories can be difficult for introductory neuroscience students to grasp. In addition, beginning students often have limited knowledge of cell biology, specifically receptor signaling. An understanding of ligand receptor interactions, and receptor signaling is an important foundation of neuronal physiology and gustatory sensation provides several cornerstone examples. The exercise outlined in this report provides students with real world

examples of the principles of gustatory sensation and perception as well as ligand receptor interactions that are garnered from personal experience.

The Indian herb *Gymnema sylvestre* reversibly inhibits the sensation of sweet presumably by blocking sucrose receptors. The herb has dual mechanisms of action, evidenced by the fact that it has been used for centuries in Ayurvedic medicine for the treatment of diabetes. Several studies have attributed the hypoglycemic effects of ingested *Gymnema* extracts to reduced intestinal glucose uptake (Shimizu et al., 1997) and increased insulin release (Baskaran et al., 1990; Persaud et al., 1999). The anti-sweet properties of *Gymnema* have been attributed to a variety of compounds including a triterpene glycoside named gymnemic acid and a 35 amino acid polypeptide (reviewed in Suttisri et al., 1995). Previous versions of demonstrations using *Gymnema sylvestre* have been published (Bartoshuk, 1974; Bolt, 2001). This report includes sample qualitative data from student subjects and highlights a sugar/aspartame taste comparison that illustrates the variety and complexity of taste receptor/ligand interactions.

MATERIALS AND METHODS

Gymnema sylvestre is inexpensive and can be purchased at specialty health food and herbal remedy stores, or through on-line specialty retailers (www.pennherb.com/cgi-bin/herbstore.cgi). The more popular capsule form of the herb will not work for this exercise due to processing and refining of the leaves in their raw form, thus the cut loose-leaf form of *Gymnema* must be used to brew a tea. Alternatively, a gum that includes the active ingredient in *Gymnema sylvestre* is also available but has not been tested by the authors (www.nancyappleton.com/pages/sfgum.htm). No more than several hours before the class meeting, prepare the *Gymnema* tea by steeping $\frac{1}{4}$ cup of the cut leaf herb in one quart of boiling water for 10 minutes. The leaves can be strained by pouring the tea through a coffee filter. The tea retains its effectiveness at a variety of temperatures and can be served cold, at room temperature, or hot. The effect of the tea is reversible and persists for approximately thirty minutes to one hour.

Begin by telling students that the tea they will be sampling will profoundly yet reversibly affect taste sensation. The effects are more dramatic if students are not told which primary taste(s) will be affected. It is not necessary to blindfold students or disguise the substances being tasted as most students will instantly recognize each substance during the initial series of tastings. Voluntary participation should be encouraged and due to the antidiabetic properties of ingested *Gymnema*, students with diabetes should be encouraged to refrain from participation. The taste of the tea itself is slightly bitter and can perhaps be best described as "spinach tea." Collection of the data presented here was approved by and in accordance with university institutional review board guidelines.

Provide each student with packets of salt, sugar, aspartame (Equal), Sweetarts, and M&Ms. Ask the

students to taste and rate each substance for the perception of sweet, sour, bitter, and salt on a scale of 0-10. A rating of "0" represents no perceived taste whereas a rating of "10" represents a very intense taste. For reasons outlined below, it is important that students taste the various substances in the following order: salt, aspartame, sugar, M&Ms, Sweetarts. Instruct the students to rinse their mouths with water between tastings to avoid any aftertaste confounds on subsequent ratings. Rinsing with water does not substantially alter or dilute the effects of *Gymnema*. Following the students' initial taste of each substance, ask them to swish an ounce of tea in the mouth for 30 seconds and then rinse with water. It is not necessary for the tea to be swallowed; however, optimal results will be obtained if all areas of the mouth are thoroughly coated prior to expectorating. Beginning with salt, instruct the students to re-taste each substance and rate and record their perception of salt, sweet, bitter, and sour tastes. The effects of *Gymnema* are profound, therefore, a simple 'first impression' of the taste of each substance is all that is needed. It is important that aspartame is sampled prior to sugar, especially for the tastings following exposure to *Gymnema*. The sensation of aspartame is only slightly altered compared to sugar; therefore, if students experience the dramatic effect *Gymnema* has on the taste of sugar prior to tasting aspartame, their perception of aspartame may be biased. The exercise can be followed with take-home questions that relate the students' personal experience with *Gymnema* to what they have learned about the theories of taste perception and taste receptor signaling.

RESULTS

During the course of the exercise, most students will report similar pre and post taste experiences for salt and will be unimpressed with the exercise at that point. However, the absence of any sweet sensation attributed to sucrose following exposure to *Gymnema* is striking, the reaction to which is entertaining to observe. Students report that sugar feels like melting sand on the tongue; Sweetarts taste exceptionally sour; and M&Ms taste chalky, salty, and bitter. The exercise leaves a profound and lasting impression on students which aids in a better comprehension of the concepts of gustation.

The responses of a typical group of 19 students are displayed in Fig. 1. Each graph shows the average rating for each substance for the sweet, salt, sour, and bitter primary tastes before and after exposure to *Gymnema* tea. Students reported little difference in their pre and post responses to salt. The dramatic effect of *Gymnema* is illustrated in Fig. 1C. All students reported a rating of "0" for the sweet taste of sugar following exposure to *Gymnema*, compared to an average rating of 9.8 prior to *Gymnema*. Interestingly, the ability of *Gymnema* to interfere with the sweet taste of aspartame was mild compared to sugar (Fig. 1C). Students reported only a 51% decrease in the sweetness of aspartame following *Gymnema* exposure with a slight concurrent increase in the salty and bitter taste components of aspartame. A comparison of the effects of *Gymnema* on the sweetness

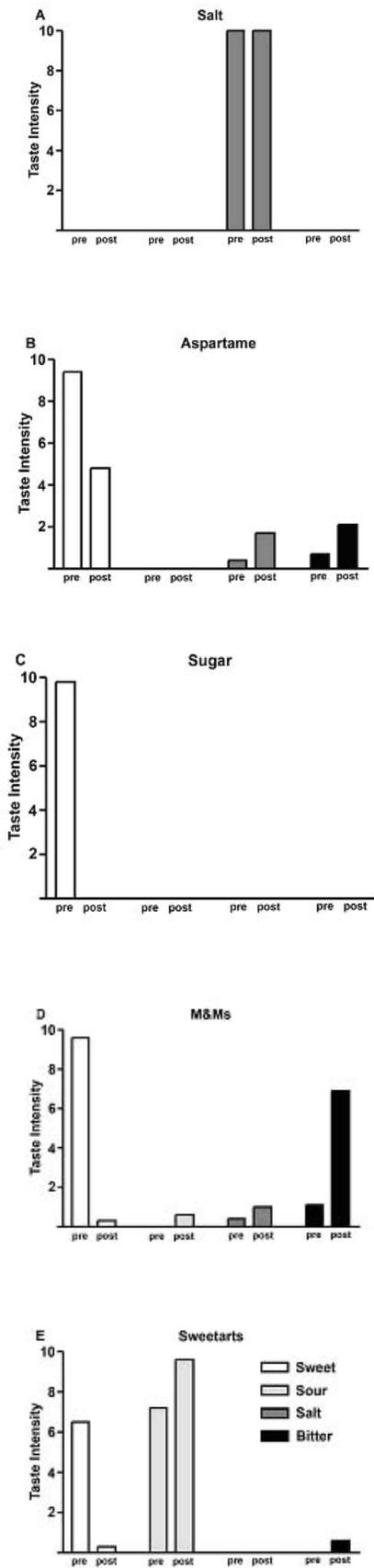


Figure 1: Mean taste ratings for salt, sugar, aspartame, Sweetarts and M&Ms prior to (Pre) and following (Post) exposure to *Gymnema sylvestri* tea. Students (n = 19) were asked to rate each substance for sweet, sour, salt and bitter on a scale of 0 (no sensation) to 10 (most intense). The dramatic alteration in the sensation of sweet is evident when comparing pre and post ratings of sugar, sweetarts, and M&Ms.

of aspartame and sugar can be used to highlight the principles of ligand receptor interaction (see discussion). Students reported Sweetarts to be much less sweet and more sour (Fig. 1E) while M&Ms were less sweet and more bitter (Fig. 1D) following exposure to *Gymnema*.

DISCUSSION

Gymnema sylvestri is a taste modulator that inhibits the ability of sucrose and other sugars to activate sweet receptors on the tongue. The effect is dramatic, reliable, reversible, and provides an effective demonstration of several important principles of gustatory sensation. Students realize from personal experience that at a basic level, there are four or five primary tastes. Combined with a lecture on the “labeled line” versus “across fiber pattern” theories of taste perception, students use their personal experience to illustrate the principles of taste perception theory. Although the concept of “labeled lines” is generally applied to gustatory afferent fibers, the concept can be extended to the receptor level for demonstration purposes using this module. Students realize that the perception of a complex taste is a combination of taste sensations from each of the four or five primary tastes, and elimination of one primary taste profile profoundly effects overall taste perception.

Aspartame is an artificial sweetener formed from a combination of the amino acids aspartate and phenylalanine and is structurally distinct from natural sweeteners. Evidence suggests that stimulation of taste cells with artificial sweeteners like saccharin results in the accumulation of intracellular calcium via an IP3 dependent mechanism whereas g-protein coupled sugar receptors activate adenylyl cyclase leading to the production of cyclic AMP and ultimately an increase in calcium through the opening of voltage-gated calcium channels (Bernhardt et al., 1996, reviewed in Gilbertson et al., 2000). The observation that sweeteners with distinctly different molecular structures activate separate signaling pathways suggests that sweet signals may be mediated by several different receptors. Recently, it has been discovered that sensation of all sweet substances, natural and artificial, is mediated by a GPCR heterodimer specific to taste cells. It is hypothesized that the receptor complex contains separate recognition sites and signal transduction mechanisms for natural and artificial sweeteners (Li et al., 2002). It can be hypothesized from the results of this exercise that the anti-sweet compound present in *Gymnema sylvestri* blocks the binding site on the sweet receptor heterodimer for sucrose but does not block the binding site for aspartame. Thus the effects of *Gymnema* on the sensation of sugar compared to aspartame can be

used to illustrate the principle of ligand receptor specificity as well as the basics of GPCR receptor signaling.

Evidence has gradually been accumulating for a fifth primary taste (reviewed in Bellisle, 1997). Umami is generally regarded as a taste described as “savory” and evidence suggests that it is transduced through activation of receptors responsive to monosodium glutamate (Chaudhari et al., 1996). The exercise outlined here could be expanded to include umami by providing students a sample of monosodium glutamate. This would serve to enhance the learning experience of taste perception as most students are unaware of the fifth umami taste.

The *Gymnema sylvestre* exercise described here can be used alone as a 20-minute in-class demonstration or part of a series of one-day laboratory exercises on the chemical senses in a mid-level undergraduate neuroscience class. For example, it can be combined with a well known taste bud visualization exercise using food coloring which can be used to demonstrate the population distribution of non-tasters, tasters, and supertasters (Miller and Reedy, 1990). The authors use the *Gymnema* exercise in conjunction with a modification of the University of Pennsylvania Smell Identification Test designed to illustrate the relationship between olfactory memory, verbal or written cues, and smell identification. Several examples of post-exercise questions posed to students include: Does your experience with *Gymnema sylvestre* support the labeled line or across fiber pattern theory of taste perception? Given what you know about receptors and based on your perception of sugar vs. Equal before and after *Gymnema*, what can you say about how each substance activates a taste cell? In addition, if the exercise is used to collect class data, the data set can be distributed to students for the preparation of a formal lab report.

Student reactions to the *Gymnema sylvestre* demonstrations are overwhelmingly positive. The exercise is referred to specifically and affirmatively in a majority of student’s course evaluations because it heightens students’ interest and investment in the course. Student comments on course evaluations include: “The herbal tea lab was a highlight of the course,” and “I never realized how losing my taste of sweet could have such an effect on my overall taste.” The exercise appears to work because the course content is directly related to student’s personal experiences – it takes learning out of the classroom and into their personal lives. Students leave the classroom discussing the profound effects of the herb and remain mesmerized by its mechanisms of action. In this way, learning leaves the classroom and continues to have its effect as students continue critical thought and reflection beyond the completion of the in-class exercise.

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