Manipulating the Gustatory System in order to Achieve Medication Adherence

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Introduction

The gustatory system is an important part of life. The gustatory system allows us the ability to perceive the world around us using taste. Through an evolutionary perspective, the sensation and perception of different taste has evolved throughout time and for our benefit. Humans and animals scavenged through their environment looking for food that provided nutrition so they could maintain a reproductive advantage. Organisms began to try many different plants in their environment, and as a result they either found nutrition or they extinguished. Over time these preferences and aversions became genetically inherited because they gave populations a reproductive advantage. Populations of organisms that did not inherit aversion to the many harmful elements in their environment most likely became extinct. Through genetics and inheritance, humans have selectively responded to five basic tastants: bitter, salty, sweet, sour, and umami. Many things in our environment that are harmful have become inherited as an aversive taste such as bitter and sour. On the other hand, many things that have nutritional value such as sweetness have become preferred. Newborns have a sucrose preference and even begin to show universal facial reactions to taste that are similar across cultures and all ages (Rosenstein & Oster, 1988).

Mennella, Bobowski, and Reed (2016) reviewed the ontogeny and biopsychology of sweet taste. A biological drive to prefer sweetness at high concentrations during childhood would have awarded an advantage in an environment of scarcity. The study reviewed the power of sweet taste to blunt expressions of pain and mask bad tastes in foods as well as factors that predispose some to consume high sugar diets. In an environment with limited nutrients and abundant poisonous plants, sensory systems
evolved to detect and prefer perceptions that specify crucial nutrients such as the once rare energy-rich plants that taste sweet, while rejecting those that taste bitter (Glendinning, 1994). Genotype explains why not all people perceive sweetness equally strong. Sweet taste receptors T1R2/T1R3 and sweet transduction protein such as gustducin are under expressed in some individuals because of genetic variation (Fushan, Simons, Slack, Manichaikul, & Drayna, 2009). Fushan et al. (2009) proposed that genetic differences in sweet taste gene TAS1R3 transcription account for a considerable amount of differences in sweet taste perception around the world. A study with children and adolescents found a common genetic factor accounted for 30% of the variance in sweet taste sensitivity to glucose and sucrose, and two nonnutritive substances (Hwang et al., 2015). But this study did not reveal whether it was the sweet taste receptor gene. So, at least for adults and older children, genotype can explain the differences in sweet taste perception (Reed & McDaniel, 2006). The sensory pleasantness derived from tasting something sweet is inborn. Age related decline in sucrose preferences might be related to the cessation of physical growth (Mennella et al., 2016).

Rarely do the basic tastants get perceived independently. The gustatory system has allowed the ability for many different tastants to be perceived in substances like foods, drinks, and medicines. The pharmaceutical industry in particular has spent lots of time and money trying to manipulate their aversive compounds into pleasant sensory experiences. Many children are not capable of swallowing pills so children require orally dispersible tablets or oral liquid medications. Many active pharmaceutical ingredients are highly aversive, which poses a concern to children. Pediatric medications such as antibiotics and antiretrovirals require strict adherence guidelines. Health professionals
need oral drug tolerance in order to maintain adherence in their patients especially in children who find many medications particularly aversive. Palatability is an important factor that pharmaceutical companies should consider when designing and refining medications through the oral route. In order to increase the palatability of medications, researchers and companies try to manipulate organoleptic features such as taste, smell, texture, and aftertaste (Walsh et al., 2014).

The current paper is a literature review on how researchers have studied methods to manipulate organoleptic features. Taste interactions are explored as a possible method. Many new methods that seem more beneficial than just masking aversive taste are cited in research. The primary research presented here primarily uses human and rat subjects but also new and upcoming taste sensor systems. The research presented here is relevant to the discussion of taste and palatability, and how these characteristics are important in the discussion of acceptability and tolerance of aversive oral pediatric medications.

The next section will review oral drug tolerance and taste-taste interactions in pediatric formulations as they relate to palatability in oral drug delivery. Taste-taste interactions to enhance the palatability of aversive pediatric formulations have been researched extensively, and some of the findings are also presented. There has been evidence to support that increasing palatability through taste-taste interaction is an important factor when considering oral drug tolerance.

**Palatability**

Palatability is one of the main elements of the patient acceptance of a medicinal product (Walsh et al., 2014). Palatability is defined as the overall appreciation of an medicine by organoleptic properties such as smell, taste, aftertaste, and texture (Walsh et
A variety of methods have been used in order to assess taste perception in children and consequently draw conclusions concerning drug palatability (Baguley, Lim, Bevan, Pallet, & Fasut, 2012). For example, taste evaluation for phenoxymethylpenicillin in children used the patient’s verbal judgment directly after the dose and several minutes later to assess drug palatability (Bagger-Sjoback & Bondesson, 1989). The purpose of the study was to assess the taste of pediatric formulations of phenoxymethylpenicillin. The test solution used aspartame and/or fructose as sweeteners and coupled this with a flavor additive of caramel, orange, or lemon (Bagger-Sjoback & Bondesson, 1989). The normal solution contained saccharine and cacao flavoring only. Researchers found that there were no significant differences between the two solutions on their taste (Bagger-Sjoback & Bondesson, 1989). Danish children older than six years yielded results that the test solution was better tasting than the original solution (Bagger-Sjoback & Bondesson, 1989). However, there were no significant differences in the taste of either solution for younger children (Bagger-Sjoback & Bondesson, 1989). Therefore researchers conclude that assessing the taste of pediatric solutions using the subject’s own verbal judgments was a beneficial way to perceive differences in taste evaluation of children older than six years old (Bagger-Sjoback & Bondesson, 1989). Also, child and parent questionnaires have been used to assess the palatability of antibiotics (Dagan, Shvartzman, & Liss, 1994). Dagan et al. (1994) assessed the acceptance and adherence to oral antibiotic solutions frequently used in Israel. A questionnaire containing eleven questions with responses such as “pleasure” or “refusal” was scored to assess acceptance, side effects, and compliance (Dagan et al., 1994). Universal, standardized visual analog scales have been used to measure children’s perceptions of oral medications. For example, Schwartz
(2000) conducted a study to gain information on how children perceive the taste of cefuroxime axetil solution by using a 5-point facial hedonic scale (Schwartz, 2000). The 5-point facial hedonic scale says that 1 is really bad and 5 as really good. Children rated the hedonic value of the solution directly after dosage and 60 seconds later (Schwartz, 2000). The study found that the taste of cefuroxime axetil solution alone was worse than amoxicillin, and that using a chocolate syrup chaser decreased the negative aftertaste and increased overall palatability to similar levels of amoxicillin (Schwartz, 2000). More complex methods have been used to assess taste perception and oral drug palatability such as electronic tongues and taste sensor systems (Baguley et al., 2012). In an experiment by Ishizaka et al. (2004), researchers conducted a study to see if a taste sensor system could predict enhancement of the bitterness of oral pediatric solutions through the addition of acidic sports drinks. The taste sensor system measures the electric potential of the drug solutions by using electrodes that contain lipid/polymer membranes (Ishizaka et al., 2004). The difference between the electric potential of the working electrode and reference electrode was measured. Researchers were able to find that the taste sensor system was able to predict bitterness enhancement that was comparable to human gustatory perceptions (Ishizaka et al., 2004). The taste sensor can measure the bitterness of many different types of antibiotics and antiviral solutions (Ishizaka et al., 2004). This method offers a new and reliable way to assess taste perception and drug palatability. Randomized control trials, like the one Schwartz (2000) conducted, are the most effective methods used to assess taste and overall treatment outcomes (Baguley et al., 2012).

Oram, Laing, Freeman, and Hutchinson (2001), investigated the ability of adults and 8-9 year old children to perceive tastes in binary mixtures. The most important
findings of the present study were that the children could only recognize one tastant above chance level in each of the binary mixtures in contrast to the adults who recognized both components (Oram et al., 2001). Therefore, children might have an underdeveloped overall appreciation for organoleptic properties that help to define palatability. Palatability of formulations, especially inhaled and pediatric ones, is very important for compliance. Thus, unpleasant and/or bitter taste of some active pharmaceutical ingredients could be detected and masked in the final preparation. Rudnitskaya et al. (2013) described how the assessment of flavor attributes is an important aspect of the development of novel pharmaceutical formulations and active substances. In this study, researchers discussed the organoleptic features of palatability that animals cannot provide information about; therefore researchers begin talking about using a taste sensor to artificially measure palatability. An electronic tongue imitates taste of animals to measure chemical components by sensor arrays. This technique is still limited in sensitivity. Much attention is paid to cell-based sensors recently. Cell-based sensor takes some advantages including fast response, excellent selectivity, and high sensitivity (Hui, Mi, & Deng, 2012). In cell-based sensors, living cells are used as the identification features to detect agents functionally with physiological changes in cells (Wang, Hui, & Deng, 2010). Mammalian cells with excitable cell membranes are used as the sensor (Wang, Hui, & Deng, 2010). Cell-based sensor systems can possibly provide researchers quantifiable organoleptic features of palatability that are similar to those of humans. Even though animals cannot describe their perception of organoleptic features of palatability, researchers have still found similar corresponding taste qualities that correspond to humans. There appears to be at least 4 categories of independent taste
qualities in the rat that correspond to those observed in humans (Grobe & Spector, 2008). Rats generalized responses to test stimuli that humans report as sweet, to sucrose (Grobe & Spector, 2008). Rats generalized quinine and citric acid to human reports of bitter and sour. Rats also generalized sodium chloride to human responses of salty (Grobe & Spector, 2008). Baguley et al. (2012) reviewed the clinical evidence around palatability with the aim of informing routine medical practice and influencing future antimicrobial guideline development. Acknowledging the importance of palatability to children and parents in patient-centered management will improve adherence and influence clinical outcome. Palatability is so significant in ensuring successful administration of a course of treatment that a recent call has been made for the evaluation of palatability and taste before European marketing authorization is granted. The taste, texture, and aftertaste of antibiotics are cited as important considerations for children taking medicines. A questionnaire study of 192 families in Japan revealed that one-quarter of patients did not adhere to the recommended dosage and that the child’s refusal behavior was the second leading cause of this non-adherence (Sunakawa, Akita, Iwata, Sato, & Fujii, 1995). Palatability was shown to be a common reason for non-adherence to treatment in children with HIV (human immunodeficiency virus) in India (Paranthaman, Kumarasamy, Bella, & Webster, 2009). In a Saudi Arabian study of 414 primary care patients, which 65.9% were children; the bitter taste of the drug was one of the reasons to non-adherence to short-term antibiotic therapy (al-Shammari, Khoja, & al-Yamani, 1995). A number of methods to improve the taste of antibiotics have been investigated and will be presented in other sections of this paper. When improving the palatability, taste masking techniques obscure the aversive taste of the active pharmaceutical ingredient/solution, or prevent
interactions of the suspended ingredients with receptors (Walsh et al., 2014). Doctors prescribing antibiotics for children need a higher level of awareness of the relative palatability of drugs (Baguley et al., 2012).

Taste-taste interactions can affect the palatability of foods, beverages, and oral medications. The purpose of Keast and Breslin’s (2003) research was to review taste-taste interactions literature while taking into account factors that could lead to contradictions. They also drew general conclusions about how tastants interact with each other. Through review they found that when assessing mixtures of taste eliciting compounds, three levels of interaction must be taken into account: chemical interactions occurring in solution, which may directly affect taste perception, secondary interactions between one of the mixture components and the taste receptors/transduction mechanisms of the other component, and cognitive effects of different taste qualities being perceived together in the mouth. Chemical interactions within a solution can affect taste perception according to Shallenberger (1993). Chemical interactions can alter the intensity of a solutions taste and can even create new taste characteristics (Shallenberger, 1993).

During oral physiological interactions, when there is a binary mixture of two compounds there is the potential for one or the other compound to interfere with the other compounds taste receptor cells or transduction mechanisms (Keast & Breslin, 2003). For example, Breslin and Beauchamp (1995) found that sodium significantly suppressed the bitterness of urea and that there is a peripheral component to the suppression of the bitterness of urea and other bitter compounds by sodium. Kroeze and Bartoshuk (1985) demonstrated this peripheral effect by conducting a split tongue taste study. A bitter compound was applied to one side of a human tongue and sodium was applied to the
opposite side. They were applied simultaneously and independently. Bitterness was only suppressed when a mixture of bitter compound and sodium were applied together on the tongue and not when independently simultaneously applied to two different sides of the tongue (Kroeze & Bartoshuk, 1985). This study also helped to explain cognitive interactions by showing that when two compounds are mixed there is suppression of individual qualities, which provides evidence that suppression had a central cognitive effect.

When two compounds with different qualities are mixed, a number of interactions may occur including non-monotonic (both enhancement and suppression) and asymmetrical intensity shifts. Binary taste interactions follow the predictions of the different phases of the psychophysical function. The literature supports the idea that three phases of a psychophysical function may be used to predict how taste stimuli will behave when mixed; low intensity/concentration mixtures tend to result in enhancement, medium intensity/concentration tend to result in additivity, high intensity/concentration tend to result in suppression.

Oral drug tolerance is important for compliance. Treatments using oral drugs or any other drug for that matter require persistent and diligent use or else the benefits of treatment are lost. Sosnik and Augustine (2016) review the challenges in oral drug delivery and innovative strategies to overcome them. The researchers proceed by saying the development of novel drug delivery systems represents a promising opportunity to overcome the various bottlenecks associated with the chronic antiretroviral therapy of the human immunodeficiency virus infection. Due to remarkable advantages such as minimal invasiveness, painfulness, ease-of-use, cost-effectiveness, reproducibility of the
administration and feasibility in the whole range of patient ages, the oral route is usually the most patient compliant. Regardless of the difficulty to ensure high bioavailability and plasma concentrations within the therapeutic window, the advantages of oral drug delivery are more prominent than the disadvantages, and thus it remains the preferred option in patients affected by chronic diseases. Even though countless efforts have and are being made to eradicate the HIV from the host, to date, the cure is not possible and a chronic combined antiretroviral therapy is required to ensure viral suppression and reduce the rate of progression from the infection to the active phase of the disease, the acquired immunodeficiency syndrome. The interaction of the drug with the gastrointestinal tract begins in the oral mucosa. Most of the antiretrovirals have undesirable taste that leads to lack of patient compliance especially in the case of liquid formulations developed for pediatric treatment, a phenomenon that in turn causes treatment failure. HIV medications are intended for chronic use and unpleasant drug taste influences the psychological well-being of the patient and favors treatment interruption. In the case of pediatric medicinal products, the selection of an appropriate and palatable liquid dosage form can make a large difference between treatment success and failure. Efforts are being devoted to develop pharmaceutical products with acceptable taste and proven safety and efficacy. Evaluation in children remains a challenge due to ethical concerns. However, this step is critical due to the greater sensitivity of the oral mucosa in younger patients.

Baguley et al. (2012) state that antibiotic adherence is an important issue in the management of any pediatric infection. The taste of an antibiotic and the child’s ability to tolerate oral drugs, although widely cited, is often not considered. Acknowledging the importance of palatability to children and parents in patient-centered management will
improve adherence and influence clinical outcome. A number of methods to improve the
taste of antibiotics and overall drug tolerance have been investigated. Erythromycin B
enol, has been proposed which has improved stability which improves taste.

Microencapsulation has been used to mask bitter tastes. Microspheres have also been an
effective method to hide taste. The unpleasant taste of many anti-retroviral drugs is well
recognized and only a minority of anti-retroviral drugs has pediatric formulations
(Baguley et al., 2012). Oral drug tolerance by adults and especially children is an
important factor that affects adherence to antibiotics.

The organoleptic features of palatability are important factors for determining
whether an oral medication will be tolerated. Taste specifically is an important feature
within palatability because it has the power to increase or decrease acceptability in
patient preference. To increase palatability researchers have done experiments using
sweet-taste interactions. Much of the research is done with sweet-taste interactions
because sweetness is able to mask bitter flavors of oral medications well.

The next section will discuss how masking has been used in prior research to
manipulate the organoleptic properties we have just discussed. Children prefer sweeter
things so if we can include sweetness into an oral medication then tolerance should
increase. However, the use of sucrose addition straight to pharmaceuticals has been
criticized and new ways to stimulate the sweet receptors are being entertained. Masking
the aversive taste of potential medications could also increase tolerance and adherence.
There are many ways to mask an aversive stimulus and some of these ways will be
presented here.

**Masking**
Sucrose, or sweeteners, has been used to mask bitter taste in oral medications. Masking the aversive tastant or compound within a medication has been experimented with a lot and is cited numerously. Taki, Tagami, and Ozeki (2016) conducted research on developing a new method to prepare nanocomposite particles in only one step, by using spray drying. Spray drying turns a liquid into a powder by quickly drying it with hot gas. This is a preferred method of drying heat sensitive pharmaceuticals. To prepare the nanocomposite particles, two solutions were spray dried through two-solution type spray nozzle. One solution was an organic solution with quinine and water-soluble polymers and the other was a mannitol aqueous solution. The results of their research concluded that the taste masking by taste sensor suggested that the polymer-blended quinine nanocomposite particles exhibited marked masking of instrumental quinine bitterness compared with the quinine nanocomposite particles alone. Quinine nanocomposite formulations altered the quinine dissolution rate, indicating that they can control intestinal absorption of quinine. The development of taste-masking technologies for foods and drugs is essential because it would enable people to consume and receive healthy and therapeutic effect without distress. These results suggest that polymer-blended quinine composite particles prepared using this spray-drying technique is useful for masking bitter tastes in the field of food and pharmaceutical industry (Taki, Tagami, & Ozeki, 2016).

Walsh et al. (2014) provided an overview of the different approaches to taste masking active pharmaceutical ingredients in pediatric oral dosage forms, and focused on the tolerability of patients used. Their overview concluded that when deciding on a choice of taste masking techniques, the researcher should take into account the
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organoleptic properties of the active pharmaceutical ingredient, in addition to its physiochemical properties. The use of sweeteners and flavors is often the first approach. The use of sweeteners and flavors is not the most effective means of taste masking however. Li, Servant, and Tachdjian (2011) also discuss sweetness and a possible sweet taste enhancer. Researchers say that excess sugar intake poses several health problems. Artificial sweeteners have been used to reduce dietary sugar content, but they are not ideal substitutes for sugar owing to their off-taste. A new strategy focused on allosteric modulation of the sweet taste receptor led to identification of sweet taste 'enhancers' for the first time. The enhancer molecules do not taste sweet, but greatly potentiate the sweet taste of sucrose and sucralose selectively. Following a similar mechanism as the natural umami taste enhancers, the sweet enhancer molecules cooperatively bind with the sweeteners to the Venus flytrap domain of the human sweet taste receptor and stabilize the active conformation. Now that the approach has proven successful, enhancers for other sweeteners and details of the molecular mechanism for the enhancement are being actively pursued.

The use of complexation with ion exchange resins or cyclodextrins is likely to be more effective than the use of flavors and sweeteners. Ion exchange resins bind to unpleasant tasting drugs and prevent connections with the active pharmaceutical ingredient and taste receptor cells (Walsh et al., 2014). Ion exchange resin particles can be suspended in a palatable solution and administered as a liquid to children. Cyclodextrins are thought to engulf the negative tasting molecules in order to decrease their interaction with the taste receptor cells. Polymeric and lipiddic coatings are considered to be the most effective techniques for masking. Bitter blockers and taste
Epigallocatechin gallate (EGCG) has been attributed to several health benefits, but its bitter taste influences the liking of products with high concentrations of this compound. Bohin et al. (2013) conducted a study where they aimed at relating the EGCG-binding characteristics of those proteins and their food-grade equivalents to their effects on reducing bitter receptor activation by EGCG in vitro and their bitter-masking potential in vivo. Their study is the first report using cell-based receptor assay setup to evaluate the reduction in activation of bitter receptors by EGCG after forming complexes with proteins. EGCG was bound to pure beta-casein, food-grade caseinates, and several gelatins to reduce the bitterness perception of EGCG. In the bitter receptor assay, Beta-casein showed the strongest effect, bitter receptors were inhibited 93%. Beta-lactoglobulin slightly reduced EGCG bitter perception. The bitter receptor assay appeared to be a valid tool to evaluate in vitro the efficacy of food proteins as complexing agents for masking bitterness (Bohin et al., 2013).

Matsui, Uchida, and Namiki (2015) studied orally disintegrating tablets of propiverine hydrochloride and how the orally disintegrating tablets were prepared using physical masking, using gastric-soluble coating particles, in combination with organoleptic masking, and with the addition of sweetener and flavor. Orally disintegrating tablets containing propiverine hydrochloride are extremely bitter and leave a feeling of numbness in the mouth. Effects of combined use of physical and organoleptic masking on metachronic palatability were evaluated in a gustatory sensation study. The results of the gustatory sensation study suggested that the visual analog scale scores of bitterness and numbness improved significantly with increasing amounts of physical
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masking, and a significant improvement in overall palatability was also noted. Visual analog scale scores for numbness increased over time regardless of the amount of physical masking. Combined use of physical and organoleptic masking is useful for improving palatability of orally disintegrating tablets containing propiverine.

In conclusion, the two themes discussed within this section were sweetness and masking. The inclusion of sweetness by natural or nutritive sweeteners can pose a problem in children. Children already have a high sucrose preference at birth so when companies use sucrose to mask food or drugs we might be increasing certain factors that predispose kids to consume high sugar diets later on in life. Guidelines and regulations are changing so that these sweeteners do not predispose children for a lifetime of sweet preferences, which could negatively affect their overall health. Masking has been a very popular technique to decrease the averseness of foods, medications etc. Through the research it seems that coatings that mask the taste of aversive compounds may be more beneficial than just trying to mask an aversive taste using sucrose.

**Binary Taste Mixtures/Suppression**

Binary taste mixtures and suppression of bitter substances like many active pharmaceuticals go hand in hand. Whenever solutions or compounds are being mixed together you are more than likely to see some form of suppression of one taste or the other tastants. The organoleptic properties of a certain tastant can potentially suppress the other tastant when they have been mixed is essentially the consensus from researchers.

Vogt and Smith (1993) recorded the extracellular activity of single third-order neurons in the hamster PbN (parabrachial nucleus) to the anterior tongue stimulation with binary mixtures of sucrose and quinine hydrochloride. They found that sucrose
suppression was prevalent among neurons most responsive to sucrose and for the mixtures that contained the stronger sucrose concentrations. Among neurons that displayed sucrose suppression, the magnitude of suppression was significantly correlated with sucrose response magnitude but not with quinine hydrochloride response magnitude. A neuron's capacity to display sucrose suppression to sucrose+ quinine hydrochloride mixtures is related to its sucrose sensitivity. Quinine hydrochloride suppression was less prevalent than sucrose suppression, and the neurons that displayed quinine hydrochloride suppression were almost exclusively a subset of those that displayed sucrose suppression to the same or different mixtures. This finding and the observation that one-third of all mixture responses involved mutual suppression suggest an association between the factors underlying sucrose suppression and quinine hydrochloride suppression.

Chen and Di Lorenzo (2008) describe in a study they conducted the electrophysiological responses to sodium chloride, sucrose, hydrochloride, and quinine as well as their undiluted binary mixtures in single cells in the NTS (nucleus tractus solitaries) of the anesthetized rat. Electrophysiological responses to four tastants and their binary mixtures were recorded from 56 cells in the NTS. For 36 of these cells, all ten stimuli were repeated at least five times. Results showed that 39% of these cells changed their best stimulus across stimulus repetitions, suggesting that response magnitude on any given trial produces an ambiguous message. Averaged across replicate trials, mixture responses most often approximated the response to the more effective component of the mixture. Cells that responded best to a taste mixture rather than any single-component tastant were identified. These cells were more broadly tuned than were cells that responded best to single-component stimuli and showed evidence of convergence from
more than one best stimulus fiber type. Functionally, mixture-best cells may amplify the neural signal produced by unique configurations of basic taste qualities.

Tokita and Boughter (2012a) investigated neural responses to umami-bitter and sweet-bitter mixtures in individual CNS (central nervous system) neurons in C57BL/6J inbred mice. Specifically, researchers investigated whether there are umami-bitter as well as sweet-bitter interactions, and whether these interactions occur in the same population of neurons. Adding quinine hydrochloride to sucrose resulted in suppression of the response in 41 of 43 synergistic neurons. The suppression ratio of sucrose and MPG (monopotassium glutamate) + IMP (inosine 5’-monophosphate) in MS1 neurons had a weak positive correlation. The pattern of reconstructed recording sites of neuron types suggested chemotopic organization in the PbN. Neurons in the medial and lateral PbN tend to respond to appetitive and aversive taste stimuli in the rat (Tokita, Yamamoto, & Boughter, 2012b). Synergistic neurons are located medially and nonsynergystic neurons are located laterally. This study found that neurons within the brachium conjunctivum as well as the medial area also respond to preferred stimuli. The researchers suggest it is a reasonable assumption that taste is organized in distinctive spatial areas of the PbN considering that chemotopic organization exist in other related taste regions of the brains of rodents (Tokita & Boughter, 2012a). Although a peripheral basis for quinine-hydrochloride suppression has been demonstrated, the results suggest that convergence in the PbN plays a role in shaping responses to taste mixtures.

Kim, Son, Kim, Misaka, and Rhyu (2015) investigated whether umami peptides suppressed bitter taste by inhibiting binding of bitter ligand to bitter taste receptors. Researchers presented umami peptides with bitter substance (salicin) on Ca$$^{2+}$$-flux
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signaling assay using hTAS2R16-expressing cells. Twenty-five hTAS2Rs, or bitter taste receptors, have been identified with the perception of bitter taste in the taste receptor cells. hTAS2R16 was used because it expresses well and is activated by a broad range of ligands. Five umami peptides derived from soybean noticeably lessened the salicin-induced intracellular calcium influx. Gly-Gly, a tasteless peptide did not. According to Ca$$^{2+}$$-flux signaling assay using the mixtures of salicin and umami peptides, all five umami peptides suppressed salicin-induced intracellular calcium influx in a noncompetitive manner. These results may provide evidence that umami peptides suppress bitter taste via bitter taste receptors. The five umami peptides bound to hTAS2R16 and interrupted the activity of the receptors agonists.

Katagawa et al. (2016) investigated whether rats recognized the components of binary mixtures when they were conditioned to aversive as well as preferred mixtures. In conditioned taste aversion tests where lithium chloride was the unconditioned stimulus, the number of licks to the preferred binary mixtures and to all tested preferred components were significantly less than in control rats. No significant difference resulted between the number of licks to the aversive binary mixtures or to all tested aversive components. Rats pre-exposed to the aversive components were conditioned to these mixtures. The number of licks to all the tested stimuli was significantly less than in controls. Results suggest that rats recognize and remember preferred and aversive taste mixtures as well as the preferred and aversive components of the binary mixtures, and that the pre-exposure before CTA is an available method to study the recognition of aversive taste stimuli.

Veldhuizen, van Rooden, and Kroeze (2006) explored the feasibility of
dissociating subjective intensity and hedonic value by proportionally mixing an unpleasant and a pleasant taste substance. Researchers used seven different concentrations of sucrose and quinine sulfate dissolved in demineralized water. Both solutions started at a near detection threshold concentration and then increased to concentrations rated as pleasant (sucrose) or unpleasant (quinine sulfate). After being cued by a beep from the computer, the subject sipped the entire solution in the cup, kept it in their mouth for 3 seconds, and then spat it into a disposal container. The subject then immediately rated the stimulus and rinsed his/her mouth thoroughly with demineralized water. After 55 seconds, the next stimulus was cued. The session was divided into two blocks per subject, one block for the quinine sulfate solutions and the other for the sucrose solutions. The total predicted intensities obtained by adding the subjective intensities of the individual components in the binary mixtures were almost but not perfectly constant. For quinine sulfate, bitterness suppression increases with increasing amounts of sucrose. For sucrose, both enhancement and suppression can be observed. The predicted subjective intensity curve of the mixture was adjusted for this mixture suppression. This adjustment considerably improved the prediction of subjective intensity. The observed pleasantness ratings varied over mixtures. Researchers were able to manipulate pleasantness in the midrange of the binary mixtures, but they could not do this independently of intensity. The study shows that subjective intensity as well as pleasantness can be accurately predicted, particularly in midrange, only if one corrects for mixture suppression.

Frijters and Schifferstein (1994) developed a study to measure bitterness, saltiness, and the total intensity of quinine-hydrochloride/sodium chloride mixtures, to
investigate how these three variables are related. It was found that the sodium chloride suppresses the quinine-hydrochloride bitterness and that quinine-hydrochloride has almost no suppressive effect on sodium chloride saltiness. The study also showed that the total intensity of the mixture percept is almost identical to the sum of the intensities of the bitterness integration within a heterogeneous percept seems to be a fairly simple additive process. It seems that the fundamental rule of central integration is independent of the nature of the taste mixture percept. In another article, Wilkie and Capaldi Phillips (2014) focus on binary interactions of heterogeneous tastants representing the taste primaries administered by aqueous solutions to human participants. Some interactions proved relatively consistent across tastants and experimental methods: sour acids enhanced saltiness, salts and sweeteners suppressed bitterness, sweeteners suppressed sourness, and sour acids enhanced bitterness. However for the majority of interactions there were differential effects based on the tastants and their concentrations. Two factors proved extremely influential in determining the perception of a heterogeneous binary taste-taste mixture. First was the concentration of each tastant. Second, although two examples might produce an identical subjective taste experience in isolation, this does not necessarily mean that they will interact the same way with other tastants.

Keast, Bournazel, and Breslin (2003) investigated whether taste interactions occur when bitter stimuli are mixed. Researchers know that the binary mixtures of two sweeteners result in a synergy of sweet taste. The binary mixture of monosodium glutamate and a sodium salt results in the synergy of a savory taste. The first experiment constructed concentration-intensity psychophysical curves for each participant and each bitter stimulus in order to mix compounds at the same perceptual level for subjects with
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different intensities. In experiment two, they wanted to see whether the binary bitter mixtures when combined would additively, became synergistic, or suppressive. The stimuli used in the study were: acesulfame-k, ammonium chloride, aspartame, citric acid, denatonium benzoate, monosodium glutamate, L-phenylalanine, sucrose, sucrose octaacetate, L-tryptophan, urea, quinine hydrochloride, ranitidine, and tetralone. The tasting protocol asked subjects to sip, rate and spit each solution. On each trial, subjects held 10 ml of solution in their mouth for 5 seconds and rated the intensity of the taste qualities of the solution (sweet, bitter, sour, salty, savory) before spitting it out. Most bitter binary mixtures combined in an additive way. The few interactions that happened were suppressive and only occurred at weak intensities. Urea was great for suppressing the bitterness of most bitter compounds. Bitter tasting compounds do not interact when in binary mixtures (Keast et al., 2003).

In conclusion, the section above has discussed research findings and literature reviews on the topics of binary mixtures and suppression. There are many different interactions possible between two tastants. Certain mixtures, like quinine sulfate, and their ability to be perceived increase and decrease when concentrations of certain tastants, like sucrose, are higher or lower. Interactions within binary taste mixtures are highly dependent on concentration and their paired tastant. Sweet has the ability to suppress many aversive bitter flavors but sweet doesn’t necessarily have the same ability when mixed with a sour tastant. Pharmaceutical companies that utilize suppression techniques increase the likelihood that consumers or patients will adhere and be able to tolerate their medications.
Discussion

The themes discussed in each section are all interrelated. Each theme discusses characteristics associated with the gustatory system. Specifically, the themes discuss manipulations of the gustatory system through interactions between tastants and more recently through complex processes that manipulate taste expression. There are probably numerous reasons why manipulations of the gustatory system are important. As we have previously stated, many tastants are not independently experienced. There is usually a complex array of taste perceived by the gustatory system. In the food world we usually mix different tastants together in order to enhance the flavor experience or to mask some other aversive one. Mixing and pairing flavors is a part of the food and beverage industry because it’s important to companies that want to have the best quality product for the consumer. Products that are highly palatable are advantageous to the businesses that produce them. Human palates have evolved and tend to seek out those positive gastronomic experiences. Another industry that manipulates the gustatory system is the pharmaceutical one. This industry tends to have a disadvantage because unlike medicines that taste bad, foods that taste bad can just be avoided. It has been noted that many active pharmaceutical ingredients are bitter and highly aversive. The pharmaceutical industry is at a disadvantage because patients require medications regardless of taste. The industry is challenged with overcoming this barrier. Overcoming this barrier is particularly important in young patients who tend to be more sensitive to aversive oral medications. The overarching theme of the review presented here is the manipulation of the gustatory system in order to increase the effectiveness of treatments for children. Oral pediatric medications such as antiretrovirals are extremely important and need to be taken
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systematically. Researchers have come a long way but there is still no perfect and highly palatable oral medication for important illnesses. The review is important for an overall understanding of how the perception of palatability by the gustatory system effects important industries, and it also provides an overview of recent literature on taste and its importance in oral pediatric medicines.

In order to increase the palatability of medications, researchers and companies try to manipulate organoleptic features such as taste, smell, texture, and aftertaste (Walsh et al., 2014). Flavors and sweeteners are the simplest way to mask an aversive bitter taste (Kaushik & Dureja, 2014). This process involves binary mixture suppression where the sweet taste masks the aversive component of the solution. However, researchers note that this method is not successful for highly aversive and soluble drugs (Kaushik & Dureja, 2014). Film coating involves coating the bitter drug to mask the taste without affecting the release time. However, this method is not perfect and the release of the drug can still be affected. Microencapsulation methods such as coacervation phase separation, spray drying, and fluid bed coating involves applying a thin coating to small bitter drug particles in order to mask the aversive taste (Kaushik & Dureja, 2014). Limitations to the microencapsulation process include low efficiency in encapsulation and organic solvents raise environmental concerns. In ion exchange resin complexation, aversive drugs can be attached to the “oppositely charged resin substrate, forming insoluble adsorbates or resonates through weak ionic bonding” (Kaushik & Dureja, 2014). This method is not intended for low pH drugs and can negatively affect onset of the drug. Cyclodextrin complexation masks the aversive drug by decreasing its oral solubility on ingestion, or it decreases the amount of aversive particles exposed to taste buds (Kaushik & Dureja,
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This method is highly dependent on the physicochemical properties of the drug however. Rheological modification increases the viscosity of the aversive liquid, which limits drug interaction with the tongue (Kaushik & Dureja, 2014). This method could prolong the duration of the aversive aftertaste however.

These methods all have their flaws and some are still in the process of being supervised and refined because the technology they use is so highly complex. Instead of manipulating the organoleptic features of the negative taste, what if we could selectively inhibit the firing of specific neurons in the parabrachial nucleus (PbN) that control the perception of bitter taste stimuli. Using a cell type-specific target to selectively inhibit the firing of neurons in the medial and lateral portion of the PbN would eliminate or decrease the bitter perception of many active pharmaceutical ingredients. Further research is still to be conducted, but once we have gustatopic maps and an idea of the chemotopic organization of specific tastants within the PbN, we will be able to selectively inhibit these areas. Even the combination of microencapsulation, ion exchange resins, or cyclodextrins with a specific C neuron inhibitor would allow the bitter particles of the active pharmaceutical ingredient to be delayed perceptually enough so that the PbN inhibitor has enough time to selectively inhibit whatever portion controls bitter perception. Children and adults who do not perceive the bitter active pharmaceutical ingredients in antibiotics and especially antiretrovirals will tolerate their medications and adhere to them more systematically, which could significantly decrease the negative consequences associated with non-adherence.
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References


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