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AN OVERVIEW ON TASTE PHYSIOLOGY AND MASKING OF BITTER DRUGS

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INTRODUCTION

Taste drives appetite and protects us from poisons. So, we like the taste of sugar because we have an absolute requirement for carbohydrates (sugars etc.). We get cravings for salt because we must have sodium chloride (common salt) in our diet. Bitter and sour cause aversive, avoidance reactions because most poisons are bitter (most bitter substances are bad for you - certainly in excess) and off food goes sour (acidic).

Taste is an important parameter in administering drugs orally. Undesirable taste is one of the important formulation problems that are encountered with many drugs. Administration of bitter drugs orally with acceptable level of palatability is a key issue for health care providers. Proven methods for bitterness reduction and inhibition have resulted in improved palatability of oral pharmaceuticals. (Narendra et al., 2004)[1]

Taste masking in defined as a perceived reduction of an undesirable taste that would otherwise exist. Although various technique are available for masking the bitter taste of drugs (Matsui, 2007; Khar et al., 2007).

The bitterness of human pharmaceutical medicines plays a critical role in patient compliance as the oral administration of bitter drugs is often hampered by their unpleasant taste, leading to noncompliance and thus decreasing therapeutic efficacy, especially in case of children and the elderly. So masking of bitter pharmaceuticals is very important (Uchida et al., 2003).

A. Physiology &Transduction mechanism :

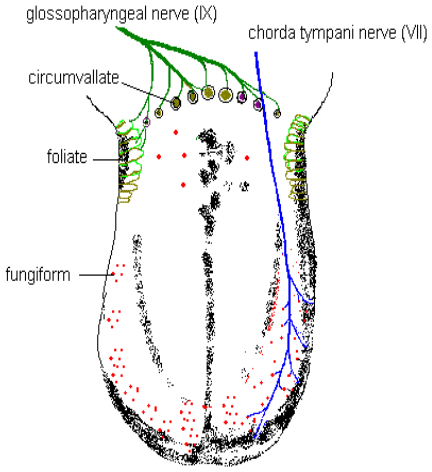

Fig.1. Tongue

Why taste is felt ? Taste drives appetite and protects us from poisons. So, we like the taste of sugar because we have an absolute requirement for carboh-ydrates (sugars etc.). We get cravings for salt because we must have sodium chloride (common salt) in our diet. Bitter and sour cause aversive, avoidance reactions because most poisons are bitter (most bitter substances are bad for you - certainly in excess) and off food goes sour (acidic).

***Anatomy and Physiology of taste*:** In mammals, taste buds are groups of 30-100 individual elongated "neuroepithelial" cells (50-60 microns[1] in height, 30-70 microns in width), which are often embedded in special structure in the surrounding epithelium, termed papillae (see Fig. 2 below). At the apex of the taste bud, microvillar processes protrude through a small opening, the taste pore, into the oral milieu. Just below the taste bud apex, taste cells are joined by tight junctional complexes that prevent gaps between cells. Food molecules cannot therefore squeeze between taste cells and get into the taste bud a micron is a thousandth of a millimetre (or 10^{-6}m for maths people)

Taste buds and taste papillae: Taste papillae can be seen on the tongue as little red dots, or raised bumps, particularly at the front of the tongue. These ones are actually called "fungiform" papillae, because they look like little button mushrooms. There are three other kinds of papillae, foliate, circumvallate and the non-gustatory filiform. You can see that the taste buds are collections of cells situated on top of, or on the sides of, the different papillae. **Figure 2** shows the taste **papillae** (on the left) - there are fungiform, foliate and circumvallate papillae. **Taste buds** are situated on the taste papillae (middle section). At the base of the taste bud, afferent taste nerve axons invade the bud and ramify extensively, each fibre typically synapsing with multiple receptor cells within the taste bud.

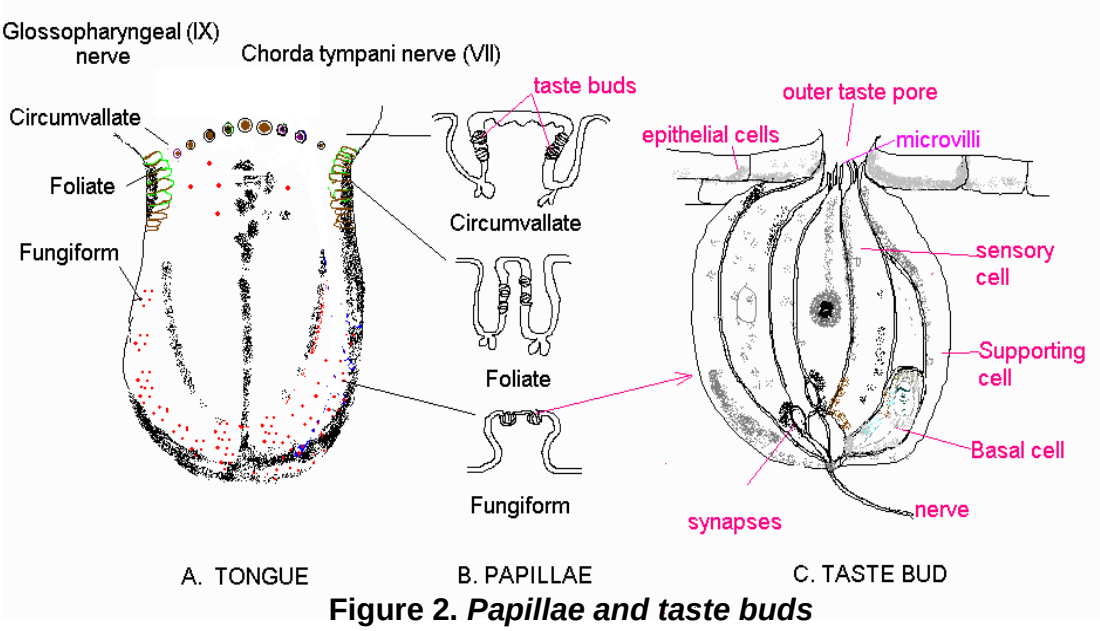

Figure 2. ***Papillae and taste buds***

In mammals taste buds are located throughout the oral cavity, in the pharynx, the laryngeal epiglottis and at the entrance of the eosophagus. Taste buds on the dorsal lingual epithelium are the most numerous (total number of taste buds, all classes, = 4600 per tongue) and best-studied taste end-organs. Here, taste buds are contained within four major classes of papillae. The number of taste buds declines with age.

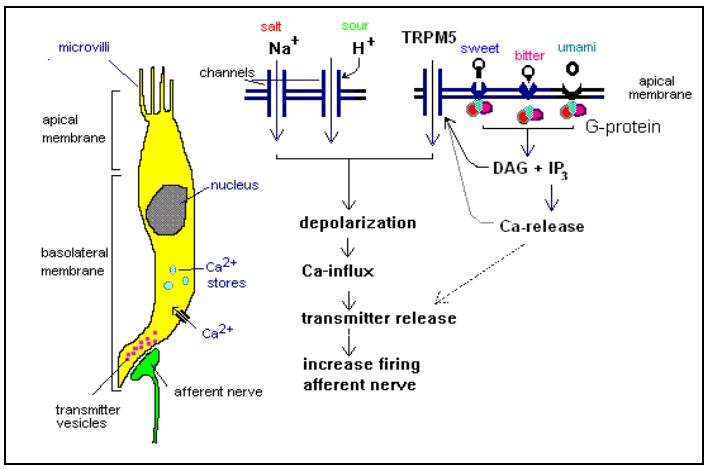

Figure 3. ***A taste receptor cell***

Taste transduction

There are five basic tastes: salt, sour, sweet, bitter and umami.

The current (as of 2008) thinking[1] is that sweet, amino acid (umami), and bitter taste converge on a common transduction channel, the transient receptor potential channel TRPM5, via phospholipase C (PLC) (see Figure 3). TRPM5 is a newly discovered TRP related to other channels in sensory signalling systems. It has been shown that PLC, a major signaling effector of G-protein coupled receptors (GPCRs), and TRPM5 are co-expressed with T1Rs and T2Rs and are vital for sweet, amino acid, and bitter taste transduction. Activation of T1R or T2R receptors by their respective taste molecules would stimulate G proteins, and in turn PLC (PLC-ß2). The activation of PLC generates two intracellular messengers - IP_3 and diacylglycerol (DAG) - from the hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP_2) and opens the TRPM5 channel, resulting in the generation of a depolarizing receptor potential. Other additional pathways may modulate sweet, amino acid, or bitter taste reception but would not, themselves, trigger a taste response. It is not at present known how PLC activates TRPM5 or whether DAG is involved. Future experiments should help reveal the G proteins for the various taste modalities and the mechanism of TRPM5 gating.

***Salt taste*:** Salt is sodium chloride (Na^+ Cl^-). Na^+ ions enter the receptor cells via Na-channels. These are amiloride-sensitive Na^+ channel (as distinguished from TTX-sensitive Na^+ channels of nerve and muscle). The entry of Na^+ causes a depolarization, Ca^{2+} enters through voltage-sensitive Ca^{2+} channels, transmitter release occurs and results in increased firing in the primary afferent nerve.

***Sour taste*:** Sour taste is acid and acid is protons (H^+). There is exciting new evidence that there is an acid-sensing channel - the PKD2L1 channel[1].This channel is a member of the transient receptor potential channel (TRP) family and is a non-selective cation channel. The activity of PKD2L1 is gated by pH (H^+ ion concentration). This new discovery displaces the previous ideas that H^+ ions block K^+ channels causing a depolarization, or that H^+ ions enter the cell through ENaC channels. These mechanisms may exist but do not lead directly to sour perception.

***Sweet taste*:** There are receptors T1R2 + T1R3) in the apical membrane that bind glucose (sucrose - a combination of glucose and fructose - and other carbohydrates). Binding to the receptor activates a G-protein which in turn activates phospholipase C (PLC-ß2). PLC generates IP_3 and diacyl glycerol (DAG). These intracellular messengers, directly or indirectly, activate the TRPM5 channel and depolarization occurs. Ca^{2+} enters the cell through depolarization-activated Ca^{2+} channels, transmitter is released increasing firing in the primary afferent nerve.

***Bitter taste*:** Bitter substances bind to the T2R receptors activating the G-protein and causing activation of PLC. The second messengers DAG and IP_3 are produced (by hydrolysis of phosphatidylinositol-4,5-bisphosphate) activating TRPM5 and mediating release of Ca^{2+} from internal stores. The elevated Ca^{2+} causes transmitter release and this increases the firing of the primary afferent nerve.

***Umami taste*:** Umami is the taste of certain amino acids (e.g. glutamate, aspartate and related compounds). It was first identified by Kikunae Ikeda at the Imperial University of Tokyo in 1909. It was originally shown[2,3] that the metabotropic glutamate receptor (mGluR4) mediated umami taste. Binding to the receptor activates a G-protein and this elevates intracellular Ca^{2+}. More recently

it has been found that the T1R1 + T1R3 receptors mediate umami taste .

***Monosodium glutamate*:** Monosodium glutamate is the main ingredient of Soy sauce. This is added to foods to enhance their flavour. As well as activating umami receptors, it probably works by activating NMDA receptors which are found in taste cells. NMDA receptors are integral receptor-ion channel complexes and when they open they allow an influx of Na^+ and Ca^{2+} ions. This will depolarise the taste receptor cell and act as an excitatory influence.

***Transmitter*:**Finger and colleagues showed that all sweet, bitter, sour, salty and umami nerve responses were lost in the purinergic double-knockout mouse. This suggests that ATP (a purinergic agonist) is the taste neurtransmitter, released by the receptor cells to activate the primary afferent nerve. The taste receptor cells release ATP in a non-vesicular fashion to activate the gustatory nerve fibres. Because the ATP is released via pannexin hemichannels rather than by vesicular fusion, Ca-influx is not necessary.

***Receptors*:** Sweet, bitter and sour taste receptors have recently been cloned. A summary of the different types of receptor responsible for each of the 5 taste modalities is given below.

Salt receptor

- ENaC (Epithelial Sodium (Na) channel)
- ubiquitously expressed

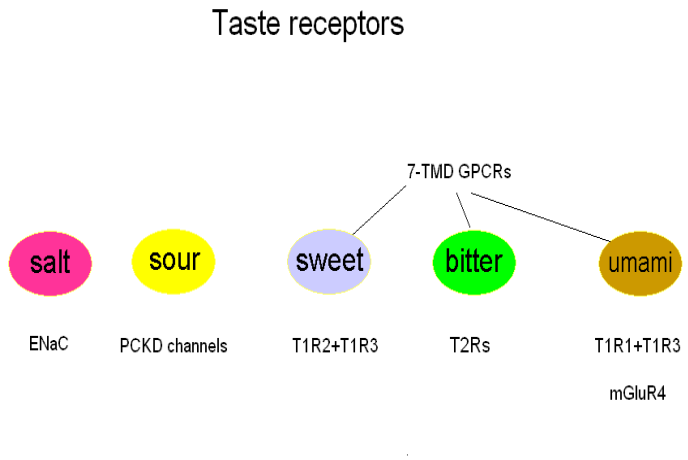

Fig. 4. *Taste receptors*

Bitter receptor family - T2Rs

- 50-80 members
- expressed in small subset of all taste papillae
- expressed in cells that also express a-gustducin
- 70% of gustducin cells in circumvallate & foliate papillae express T2Rs

***Sweet and umami receptors* :** Heteromeric receptors made up of a combination of different subunits, coded for by a small gene family - T1Rs - have a look at their structure

- T1Rs (3 genes distantly related to mGluRs)
- By in situ hybridization, Liao and Schultz (2003) found that all 3 T1R genes are expressed selectively in human taste receptor cells in the fungiform papillae, consistent with their role in taste perception.
- T1R1+3 = amino acid receptor (umami)
- T1R2+3 = sweet receptor
- T1R3 - on its own may be the sweetner receptor
- Umami is possibly mediated by both mGluR4 and T1R1+3 receptors

***Sour receptors*:** Sour is the taste of acid, i.e. protons (H^+). In August 2006, Huang et al published a paper showing that mice in which cells expressing PKD2L1 (polycycstic kidney disease-like channel) were ablated (knocked out) were completely unable to detect sour substances. PKD2L1 is a member of the TRP (transient receptor potential) superfamily of ion channels. They are non-selective cation channels. PKD2L1 is gated by pH (H^+ ion concentration), a decrease in pH (acidity) openingthe channel and causing a depolarizing receptor potential. This activates voltage-dependent Ca^{2+} channels, evelating intracellular Ca^{2+} . This in turn causes the release of transmitter (now thought to be ATP).

***Artificial Sweetners*:** Have a look at the structure of sweetners - most sweetners have a structure very different from that of sweet tasting compounds, e.g. glucose.

1. Saccharin- Discovered in 1879 when a Johns Hopkins worker inadverently licked his fingers. Saccharin is only sweet to humans. Bees/butterflies which normally crave the sweetness of nectar, do not treat it as a desirable substance.

2. Cyclamate –Discovered by accident. A graduate student at the University of Illinois in 1937 was smoking a cigarette that came into contact with some.

3. Aspartame – James Schlatter licked fingers in preparing to pick up a peice of weighing paper. It is a combination of two naturally occurring amino acids (aspartic and phenylalanine). Alitame, similar to aspartame in that it combines two amino acids (alanin and aspartic acid) into a dipeptide, is about 2,000-times sweeter than sugar.

4. Sucralose – A chloride-containing carbohydrate product some 600-times sweeter than sugar. Discovered when a foreign student (Shashikant Phadnis) working in Prof Leslie Hough's lab at King's College, London, misunderstood a request for "testing" as "tasting".

Some plant proteins, e.g. Monellin and Thaumatin, taste 10,000 times as sweet as sucrose (a disaccharide made up of a glucose and a fructose molecule). Salts of lead and beryllium also taste sweet.Certain artifical sweetners (e.g. saccharin) lead to the generation of IP_3 and a rise in intracellular Ca^{2+} due to release from internal stores.

Modifying taste: Taste exhibits almost complete adaptation to a stimulus - perception of a substance fades to almost nothing in seconds. Taste can be suppressed by local anaesthetics applied to the tongue. Amiloride, a blocker of epithelial Na channels, reduces salt taste in humans and adenosine monophosphate (AMP) may block the bitterness of several bitter tasting agents. Naturally occuring compounds include, gymnemic acid (a product of the Indian tree/shrub Gymnema sylvestre) decreases the sweet perception by competitive inhibition of the sweet receptor.

***Relay to the brain*:** Taste receptor cells do not have an axon. Information is relayed onto terminals of sensory fibres by transmitter. These

fibres arise from the ganglion cells of the cranial nerves VII (facial - a branch called the chorda tympani)) and IX (glossopharyngeal) (see Figure 5).The first recordings from sensory fibres showed an optimal response to one stimuli, but a smaller response to other taste stimuli.

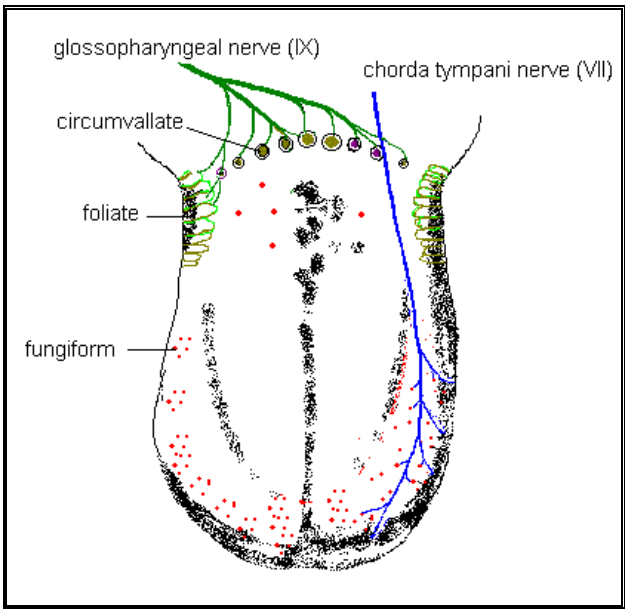

Figure 5. ***Innervation of the tongue***

***Central pathways*:** Primary gustatory fibres synapse centrally in the medulla (in a thin line of cells called the nucleus of the solitary tract). From there the information is relayed (1) to the somatosensory cortex for the conscious perception of taste and (2) to the hypothalamus, amygdala and insula, giving the so-called "affective" component of taste. This is responsible for the behavioural response, e.g. aversion, gastric secretion, feeding behaviour.

***Supertasters*:**It has been found that some people have more than the normal number of taste papillae (and taste buds). They are distinguished by their increased density of fungiform papillae and their exterme sensitivity to the chemical n-propylthiouracil (PROP). Supertasters - 25% of the population (and more women than men) - tend not to like green vegetables and fatty foods.

***Strange taste facts*:** Taste is mainly smell. Hold your nose, close your eyes, and try to tell the difference between **coffee** or **tea**, **red** or **white** wine, **brandy** or **whisky**. In fact, with blocked nose (clothes peg or similar) you can't tell the difference between grated apple and grated onion - try it! Of course, this is because what we often call taste is in fact flavour. Flavour is a combination of taste, smell, texture (touch sensation) and other physical features (eg. temperature).

***Taste Masking Technologies of bitter pharmaceuticals*:** The term ‘‘flavor’’ is used to describe the taste of any particular food or drink[5] and the sensation of taste, a chemical sense, can be expressed as a feeling by an individual when something is put into the mouth in order to

ascertain the wholesomeness of the component. Four fundamental sensations of taste have been described:. Sweet and salty, mainly at the tip. . Sour, at the sides. . Bitter, at the back. Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist. The ideal solution to reduce or inhibit bitterness is the discovery of a universal inhibitor of all bitter tasting substances that does not affect the other taste modalities such as sweetness or saltiness. Two comprehensive reviews to control bitter taste have already been presented along with thoughts on the discovery of a universal bitterness inhibitor.

TASTE MASKING TECHNIQUES OF BITTER PHARMACEUTICALS

Bitterness reduction and inhibition are important characterristics of a good oral dosage form. Considerable amount of progress has been achieved in the development of taste-masked formulations in recent years. Proven methods for bitterness reduction and inhibition have resulted in improved palatability of these formulateons. Development of oral pharmaceuticals as replacements for normally injectable peptides may become increasingly common if reduced bitterness can be accomplished to a certain extent. Anappreciable amount of success has been achieved in the development of bitterless, tasteless, and taste-masked formulations in recent years.

1. Taste Masking by using Flavors and Sweeteners: This technique is the foremost and the simplest approach for taste masking, especially in the case of pediatric formulations, chew-able tablets, and liquid formulations. But this approach is not very successful for highly bitter and highly water soluble drugs. Artificial sweeteners and flavors are generally being used along with other taste-masking techniques to prove the efficiency of these techniques. Numerous harmaceuticals such as dentifrices and mouthwashes plied to the oral cavity elicit unpleasant taste perceptions.

2. Taste Masking with Lipophilic Vehicles like lipids and lecithins: Oils, surfactants, polyalcohols, and lipids effectively increase the viscosity in the mouth and coat the taste buds, and therefore they are potential tastemasking agents. Guaifenesin has improved taste when mixed with carnauba wax and magnesium aluminium silicate and then melt-granulated. The taste of cimetidine can be improved by granulating it with glyceryl monostearate.

3. Taste Masking with Hydrophilic polymer coating: This is the simplest and most feasible option to achieve taste masking. The coating acts as a physical barrier to the drug particles, thereby minimizing interaction between the drug and taste buds. Coating of chewable tablets provides excellent taste masking while still providing acceptable bioavailability. A cialized technique, i.e., micro emulsion technology, has been used for taste masking of powders, chewable tablets, and liquid suspensions .

4. By using effervescent agent: Effervescent agents have been shown to be useful and advanta-geous for oral administration of drugs and have also been employed for use as taste-masking agents for dosage forms that are not dissolved in water prior to administration. A chewing gum composition of bitter medicament(s) was formulated to supply the medicament(s) to the oral cavity for local application or for buccal absorption.

5.By salt Preparation of bitter drugs: Adding alkaline metal bicarbonate such as sodium bicarbonate masks the unpleasant taste of water-soluble ibuprofen salts in aqueous solution. The bitter taste of caffeine may be masked by formulating it as a carbonated oral solid preparation using sodium bicarbonate, ascorbic acid, citric acid, and tartaric acid. Magnesium aspirin tablets are rendered tasteless by preparing magnesium salts of aspirin.

6. Masking by Solid Dispersion Systems: Solid dispersions can be defined as the dispersion of one or more active ingredients in an inert solid carrier. Solid dispersion of drug with the help of polymers, sugar, or other suitable agents, is very useful for taste masking. The bitter taste of dimenhydrinate can be masked by preparing the solid dispersion of the drug with polyvinyl acetate phthalate.

7. Prodrug Approach: The alkyloxyalkyl carbonates of the clarithromycin 2' position have remarkably alleviated bitterness and improved bioavailability when administered orally. Tasteless/bitterless prodrugs of opioid analgesics and antagonists were formulated for improved buccal delivery. Tasteless prodrugs of nalbuphine HCl, naltrexone, naloxone, oxymorphone HCl, butorphanonol, and levallorphan were synthesized for buccal adminis-tration to improve bioavailability relative to that of oral dosing without the characteristic bitter taste.

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