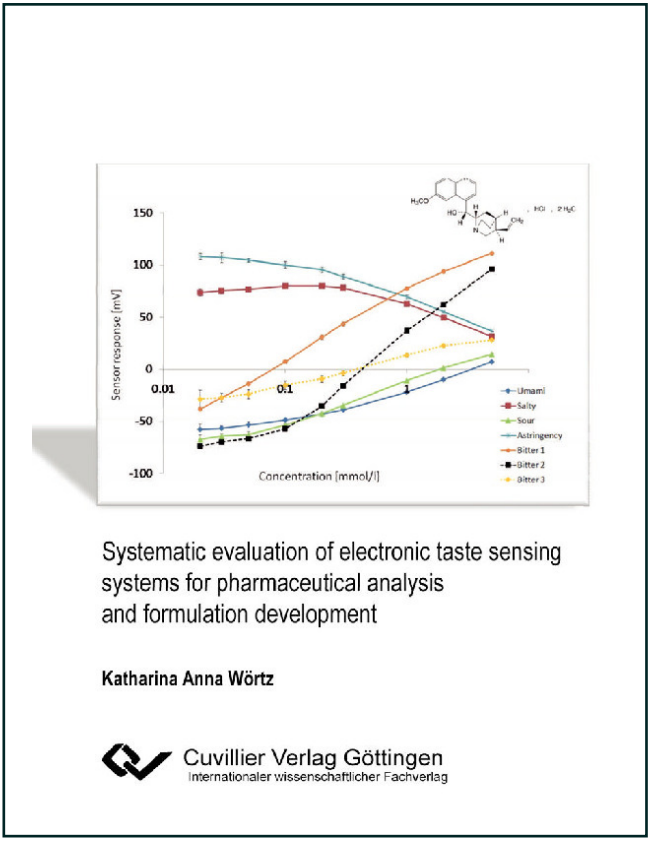
Katharina Wörtz (Autor)

Systematic evaluation of electronic taste sensing systems for pharmaceutical analysis and formulation development



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CHAPTER 1 - INTRODUCTION

1. Physiological background of taste sensation

Taste is one of the vertebrate's basic five senses and a highly developed mechanism to detect characteristics of substances administered to the oral cavity. From an evolutionary point of view, this important sense enables the vertebrate to judge over essential substances, like for example electrolytes, which are often detected as salty or weakly sour, or carbohydrates, which are often sweet. But, it also serves as a warning system to prevent intoxication by specific substances which are often associated with bitter or strongly acidic taste (Boughter and Bachmanov, 2008). Taste sensation is influenced by various factors. In addition to the interaction of taste substrates with receptors on the tongue, the olfactory system and thermo-mechanical sensors are involved to a large extent. After receptor binding, signal cascades evolve and are processed by the neural network. Here, processes of recognition and association play an important role as well as adaptation to substances which are frequently tasted (Wolfe et. al, 2009). Generally, five basic taste sensations are known: salty, sour, sweet, bitter, and umami. Umami is the Japanese wording for pleasantness or palatability and is typically mediated by the substance monosodium glutamate. In addition, nociceptive sensations like astringency or pungency are recognized on the tongue as well as general mouth feelings like smoothness for example.

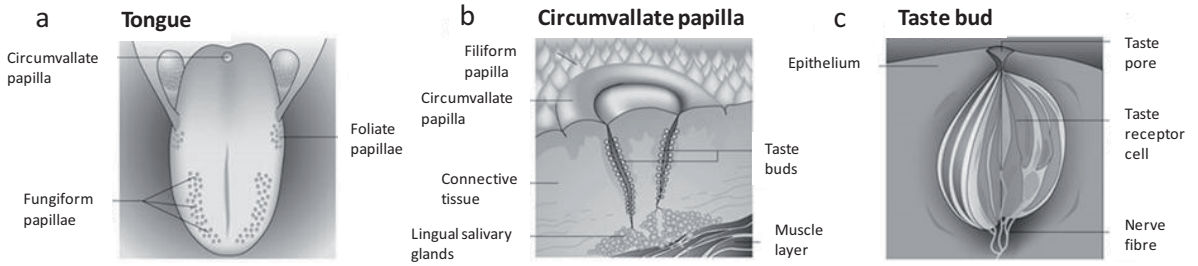

Fig. 1. Taste sensing systems on the human tongue (Mombaerts, 2004).

Compounds dissolving at the pH of saliva (typically 5.8 – 7.4) interact with taste receptors and elicit a response. The intensity of taste sensation is generally influenced by two processes. First, the interaction of a certain concentration (C) of the taste substrate with a taste receptor cell (TRC). It can be described by the concentration-response (R) function and takes the form of the law of mass action $R = R_m C \ / \ (k_d + C)$, where R_m is the maximal response and k_d is the apparent

receptor/ tastant dissociation constant (DuBois et al., 2008). Second, after binding, the Weber-Fechner-Law applies, which provides that the perceived magnitude of stimulus is proportional to the logarithm of the intensity of the stimulus (Johnson et al., 2007).

A number of receptors and receptor types are responsible for differences in taste sensation. Taste receptors cells are located in taste buds, which are collections of approximately 100 cells, clustered within an onion-shaped structure (Gilbertson et al., 2000). These taste buds can be found in different types of papillae on the tongue (Fig. 1). While saltiness and sourness are generally mediated via ion channels, G-protein coupled receptors are responsible for transmission of taste sensations like bitterness, sweetness, and umami (Fig. 2). Furthermore, various subtypes of TRCs have been identified from different receptor families. For example, there are estimated 40 - 80 different receptors of the T2R family in humans mediating bitter taste via a G-protein called gustducin (Gilbertson et al., 2000).

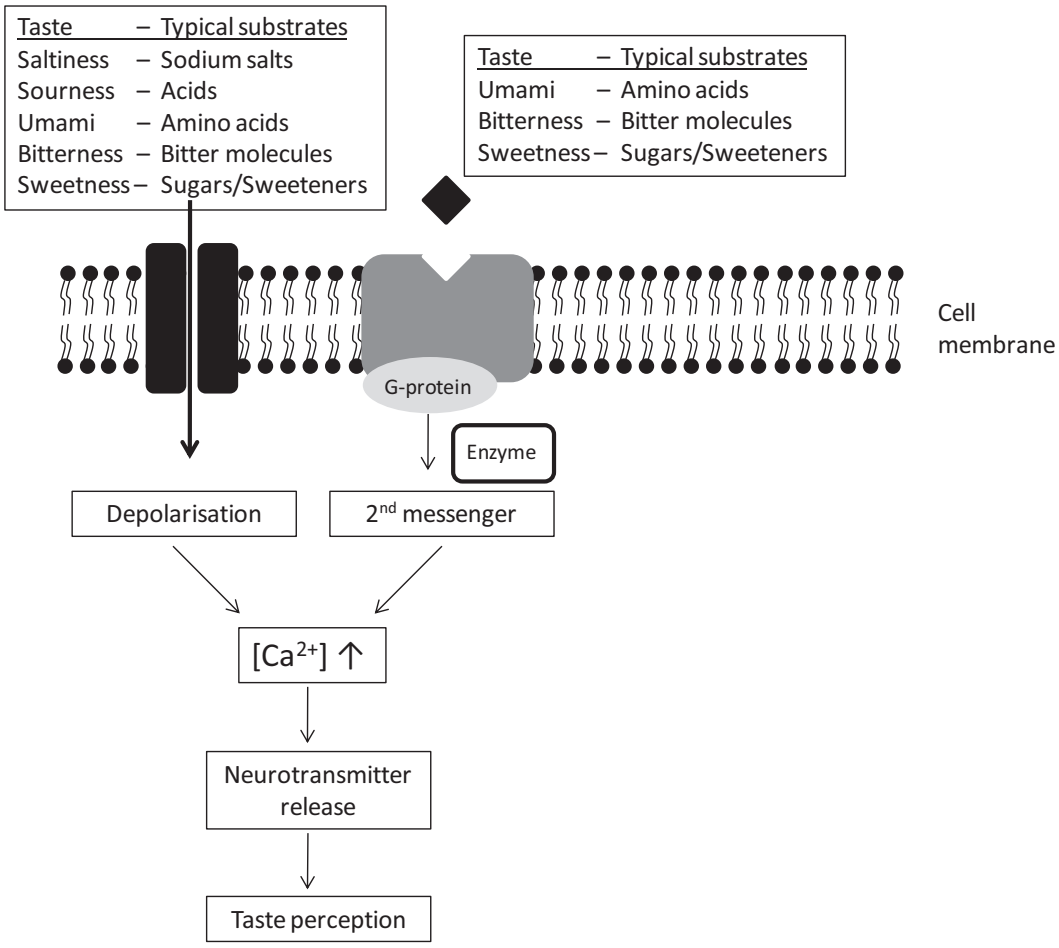

Fig. 2. Physiology of taste transduction (simplified according to Gilbertson et al., 2000).

After binding to the receptor or transmission via ion channels, the cell depolarizes and Ca^{2+} is released, either directly in the case of ion channel transduction, or after activation of gustducin and production of the second messengers inositol triphosphate (IP3) and diacylglycerol (DAG). Subsequently, neurotransmitters are released and nerve impulses are transmitted to the brain resulting in a corresponding taste perception (Kinnamon and Margolskee, 2008).

There is a large variation of quantitative and qualitative taste perception in between different individuals. One reason is that the expression of different TRCs can vary due to individual genetic code. There are so called non-tasters, which do not taste, for instance, the bitter taste of phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP). In addition, individuals, which experience not only the greatest bitterness from PROP but also huge taste intensities from other taste stimuli, are defined as supertasters (Snyder et al., 2008). Also personal constitution plays an important role as smoking, diseases, or the intake of medication for example may have an influence on taste perception (Bartoshuk, 2000). In addition, human taste sensation is subject to adaptation processes due to frequent exposition to certain substances, meaning that desensitization to certain taste qualities can occur. On a receptor level, this can be explained by receptor phosphorylation by kinases which are specific for actions on G-protein coupled receptors (DuBois et al., 2008).

Therefore, taste sensing remains subjective and especially children are, from an evolutionary point of view, more sensitive to bitter taste, as bitter substances are often associated with toxicity (Kinnamon and Margolskee, 2008). This sensitivity usually decreases with age but nevertheless, the administration of bitter tasting substances may be challenging.

2. Unpleasant taste of active pharmaceutical ingredients

All chemical compounds, organic, inorganic, or organometallic, exhibit taste and are therefore potential gustatory stimuli (DuBois, 2008). Furthermore, many active pharmaceutical ingredients (APIs) have an unpleasant bitter taste and a nociceptive feeling, which can be expressed as spicy, peppery, or metallic. The European pharmacopoeia uses a simple test for bitterness quantification, also known as determination of the bitterness value, which offers a rough classification of pharmaceutical molecules. It is defined as the reciprocal value of the dilution of a compound, a liquid or an extract which still has a bitter taste (European Pharmacopoeia, 2011). However, as described in section 1, bitterness comes along with different qualities and is therefore hardly ratable in a valid manner. To date, it has not been fully understood which molecular characteristics lead to a certain taste

of a substance. There are investigations showing that the presence of nitrogen atoms, for example, often leads to bitter taste or that sweetness is caused by the presence of –OH groups in the molecule, but an all-embracing explanation has not been found yet (Rodgers et al., 2005). This fact makes it difficult to predict the taste of a substance and to reduce or mask unpleasant taste of substances based on a general approach.

Two unpleasant tasting active pharmaceutical ingredients were used in this thesis in order to mask their taste, quinine hydrochloride and ibuprofen. The differences in molecular characteristics and solubility require different considerations in terms of formulation development and taste masking.

2.1 Quinine hydrochloride

Quinine hydrochloride (Fig. 3) is one of the bitterest natural molecules, which is mainly used for the treatment of malaria in paediatrics and the therapy of cramps in the calf. Its bitterness value is 200 000, meaning, that 1 g of the substance diluted in 200 l of water is still detected with a bitter taste. Due to its sharp bitterness it is also added to beverages, like aperitifs or grapefruit juices. It is further used as reference substance for calibration of volunteers of a human taste panel according to the European Pharmacopoeia. Quinine hydrochloride is highly soluble in water, 62.5 g/l at 20 °C (Caelo, 2010), leading to fast molecule-taste receptor interaction and therefore to special considerations regarding taste masking techniques.

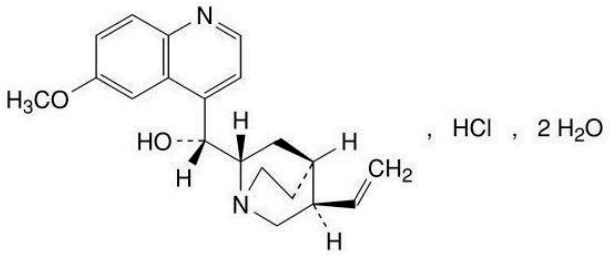

Fig. 3. (*R*)-Quinine hydrochloride (Ph.Eur.).

2.2 Ibuprofen

Ibuprofen (Fig. 4) belongs to the group of non-steroidal anti-inflammatory drugs (NSAIDs) and is mainly used for the treatment of fever, pain, and rheumatic diseases for adults as well as for the paediatric population. In contrast to quinine hydrochloride, its taste is described as bitter, sour and peppery (Reader et al., 2006). The bitterness value according to the European Pharmacopoeia is 100 000.

Ibuprofen is a weak acid (pk_s = 4.42) with poor solubility in water. Depending on the pH solubility varies from 0.03 g/l – 180 g/l (Avdeef, et al., 2000).

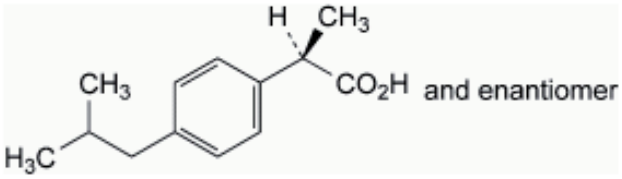

Fig. 4. *(RS)*-Ibuprofen (Ph.Eur.).

3. Taste masking of unpleasant tasting active pharmaceutical ingredients

The unpleasant taste of an API might lead to rejection of the medicine or compliance issues especially in children, which can dramatically decrease the success of drug therapy. As recent changes in the European regulatory requirements (Regulation (EC) No 1901/2006, 2006) demand the development of age-appropriate formulations adequate for the use in the paediatric population, taste masking of unpleasant tasting drug substances has become even more important during the past years. Another critical aspect is the administration of unpleasant tasting APIs to animals, which have been found to be sensitive to unpleasant tasting substances, depending on the species, even more than humans are. As described in section 1, the olfactory sensation mainly contributes to the overall taste sensation. As a lot of animals are very sensitive to different odors, they might reject the medicine, often administered with food, before even trying. Whereas children might be convinced by their parents to take the medicine in order to recover soon, some animals will be hardly convincible. Therefore, the administration of an unpleasant tasting drug might lead to even more difficulties in this special case. For these reasons taste masking plays an important role in the development of paediatric medicines and veterinary medicines as well. According to a patent review, there were 76 new patents and 108 patent applications dealing with different taste masking techniques in the years 1997 - 2007 indicating the importance of this particular field (Ayenew et al., 2009).

There are different techniques available in order to mask the unpleasant taste of a drug. The appropriateness of a certain technique for a particular API depends on various factors, like for example the extent of bitter taste, particle shape and size, solubility, ionic characteristics, but also the intended dosage form and compatibility of taste masking excipients (Ayenew et al., 2009).