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Quantitative prediction of bitterness masking effect of high-potency sweeteners using taste sensor

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ABSTRACT

A taste sensor based on lipid/polymer membranes has been reported being possible to detect the masking of bitter substances or masking on bitterness receptors (physical masking or biochemical masking). However, it was difficult to express the bitterness suppression by sweeteners, which is decided by the balance of substances produced in human's brain (functional masking). High-potency sweeteners are one of the sweeteners used for bitterness-masking in food and pharmaceutical industry. The objective of this study is to evaluate the bitterness-masking effect of high-potency sweeteners using the taste sensor. A bitterness sensor was used to evaluate the bitterness of quinine hydrochloride, and sweetness sensors for high-potency sweeteners were used to evaluate the sweetness of aspartame and saccharine sodium. The sensory evaluation was also carried out to examine the bitterness suppression effect of high-potency sweeteners. The bitterness-prediction formulas were proposed with the aid of a model regression analysis using two outputs from the bitterness sensor and the sweetness sensor for high-potency sweeteners. As a result, the predicted bitterness showed a good correlation with the human taste when aspartame or saccharine sodium was added to quinine hydrochloride. Thus, this study provided an effective method to evaluate the bitterness suppressed by high-potency sweeteners.

1. Introduction

The patients' quality of life (QOL) has become a significant issue, especially in the aging society with a lower birth rate. In order to provide a pleasing drug therapy, bitterness-masking is becoming an essential part of pharmaceutical development. Various technologies have been developed to mask bitterness of drugs, especially for orally disintegrating tablets and dry syrups containing a bitter drug substance. The methods of masking bitterness could be divided into three types: physical masking, biochemical masking and functional masking [1]. Physical masking is one of the most important and commonly used bitterness masking method. A polymer or microencapsulation is used as a physical barrier to separate bitterness component from taste receptors [2]. Biochemical masking methods are well known as chemical modification including prodrug or cyclodextrin interact by inclusion [3]. Functional masking is one of the simplest techniques used in taste masking. Sweeteners, flavorings and other excipient additions have been usually used as additives to suppress the bitterness. Because of rich kinds of sweeteners including those food additives, sweeteners are playing a central role among all the additives [4,5].

Sweet substances include many kinds of compounds with various chemical structures, for example, sugars (sucrose, glucose), sugar alcohol (sorbitol, mannitol and xylitol), peptide (aspartame) and protein (monellin). In terms of human receptors, T1R2/T1R3 heterodimeric receptors respond to both diverse natural and synthetic sweeteners [6–8]. The sweetener potency of a sweetener is defined as the ratio of the concentration of sucrose versus an equal-sweet concentration of the sweetener. Sweeteners, such as sucrose and glucose are known as low-potency sweeteners, with sweetener potencies about 1 and less (0.6–0.7). On the other hand, sweeteners which have a sweetener potency exceeding 10 are called high-potency sweeteners, such as saccharin sodium and aspartame. For some low-potency sweeteners like sucrose and xylitol, the sweetness intensity increases with higher concentrations. Interestingly,

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even though the same effect occurs at low concentrations of high-potency sweeteners, the increase in sweetness intensity slows to an eventual plateau at high concentrations of high-potency sweeteners. That is the reason why low-potency sweeteners are also called high-intensity sweeteners [4,9,10]. Because of these properties, low-potency sweeteners (such as mannitol and sorbitol) and high-potency sweeteners (such as aspartame and saccharine sodium) were usually used together in pharmaceuticals to supplement sweetness and improve drinking ease [4,11]. In this study, we choose aspartame and saccharine sodium, which are two main high-potency sweeteners used in drugs.

Although the addition of sweet substances is the most conventional approach to mask bitterness, the mechanism of bitterness suppression using this method has not yet been fully explained. Manabe et al. [12] reported the activities in rat cerebrospinal fluid after feeding bitterness and sweetness solutions. Their research suggested that diazepam binding inhibitor (DBI) was released in the brain after feeding the rat with quinine hydrochloride; on the other hand, β- endorphin was detected in the brain after feeding the rat with sucrose and saccharin [13]. The balance of these substances leads to a suppression effect such as bitterness suppression [14]. To evaluate the suppression effect caused by functional masking, sensory test is necessary in general case. However, it is difficult to carry out sensory tests frequently, because of some problems such as low objectivity, low reproducibility and potential for side effects of drugs.

In order to evaluate the taste objectively, many researches for electronic tongues [15–17] and a taste sensor [18] have been carried out so far. The taste sensor is referred to an electronic tongue with a global selectivity. Here, global selectivity is defined as the decomposition of the characteristics of a chemical substance into taste qualities and their quantification, rather than the discrimination of individual chemical substances. Therefore, each sensor electrode of the taste sensor outputs a kind of taste and also expresses the intensity of the corresponding taste [19].

A commercialized taste sensor (Taste sensing system, Intelligent Sensor Technology Inc., Japan) is composed of a number of functional sensor electrodes with lipid/polymer membrane of different compositions. The composition of the membrane is designed by considering the electric charges on the membrane surface and the hydrophobicity on the basis of physicochemical properties of substances with each basic taste [18]. By adjusting the composition of membrane, each sensor electrode is able to identify a specific taste, i.e., saltiness, sourness, sweetness, bitterness or umami, and quantify taste intensities corresponding to human gustatory sensation [19]. For example, bitter substances with high hydrophobicity are adsorbed onto the oppositely charged membrane with highly hydrophobic characteristic as well. This system has been used to evaluate the taste of various foods and beverages (e.g., coffee, beer, mineral water and tea) [18–21] and has been able to detect the suppression of bitterness of quinine hydrochloride and a drug substance for asthma by sucrose [22]. In addition, the taste sensor succeeded in expressing the suppression effect caused by a commercial bitterness masking substance (BMI-60, Kao Company, Ltd.), which is a phospholipid cocktail with almost no taste [23]. However, it was difficult to express the bitterness suppressed by adding sweet substances, which was decided by the balance of substances produced in human's brain [14,24]. Therefore, a quantitative method of predicting a bitterness masking effect using sweeteners has not been developed so far. Due to the data from Pharmaceuticals and Medical Devices Agency (PMDA), 25% of commonly used oral formulations include aspartame and saccharine, which implies that the high-potency sweeteners are widely used in masking bitterness in pharmaceutical industry [4].

Recently, we have developed two kinds of sweetness sensors; one is for positively charged high-potency sweeteners such as aspartame [25] and the other one is for negatively charged high-potency sweeteners such as saccharin sodium and acesulfame potassium [10]. Therefore, the sweetness of high-potency sweeteners can be evaluated by using these two sweetness sensors for high-potency sweeteners. On the other hand, the bitterness of drug products without containing sweeteners can be evaluated using a bitterness sensor [18–20,26–28].

In this study, we proposed the estimate formulas to evaluate the masking effect of high-potency sweeteners by regression analysis, using the outputs of the bitterness sensor and the sweetness sensors for high-potency sweeteners.

2. Materials and methods

2.1. Chemicals

Quinine hydrochloride was purchased from Kanto Chemical Co., Inc., Tokyo, Japan. Aspartame was donated from Ajinomoto Co., Inc. and saccharine sodium as well as acesulfame potassium was purchased from Tokyo Chemical Industry Co., Ltd. The samples used in the sensory test were obtained from the same company just like the sensor experiment. The chemical structures of these chemicals are shown in Fig. 1. Saccharine sodium is negatively charged. Aspartame and quinine hydrochloride are positively charged when dissolved in solution.

2.2. Taste sensor

A commercialized taste sensing system (TS-5000Z, Intelligent Sensor Technology Inc., Japan) is composed of a number of functional sensors, where a lipid/polymer membrane is fixed to the sensing part of each sensor electrode. The lipid/polymer membranes comprising a lipid, PVC and a plasticizer respond to each basic taste according to the concentrations and combination of the lipid and the plasticizer [19,27]. A bitterness sensor [26] and the sweetness sensors [10,25] for high-potency sweeteners were used in this study. The membrane components of the sensors are listed in Table 1.

The reference electrode and sensor electrodes comprise an Ag/AgCl electrode and an inner solution containing 3.33 M KCl and saturated AgCl. The voltage difference between the sensor electrode and the reference electrode was measured. First, the sensor electrodes were immersed in the reference solution of 30 mM KCl and 0.3 mM tartaric acid, which mimics human saliva with almost no taste [29]. The membrane potential of reference solution was obtained as V_r. Second, the sensors were immersed into a sample solution to obtain V_s. Third, the sensors were immersed into the reference solution again to obtain V_r' after being lightly rinsed by the reference solution. The difference between potential ($V_s - V_r$) is called the relative value. The difference between potential ($V_r' - V_r$) is called the CPA (the Change in the membrane Potential caused by Adsorption) value [18–21,30]. Finally, the membrane was rinsed with a sensor-rinsing solution that consists of 30 vol% ethanol, 100 mM KCl and 10 mM KOH for the sweetness sensor to measure negatively charged sweeteners. The sensor-rinsing solution for the sweetness sensor for positively charged sweeteners and bitterness sensor consist of 30 vol% ethanol and 100 mM HCl Fig. 2.

2.3. Matrix effect of sensor responses in mixture of quinine hydrochloride and high-potency sweeteners

The change of sensor responses caused by the coexisting substances except for the measuring substances is called matrix effect [31]. For the bitterness sensor, high-potency sweeteners are the coexisting substances in this study. To investigate the matrix effect of the bitterness sensor, we prepared the mixture solutions which