Reviews

Taste sensor: Electronic tongue with lipid membranes

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Abstract

Taste is of five basic types, namely, sourness, saltiness, sweetness, bitterness and umami. In this review, we focus on a potentiometric taste sensor that we developed and fabricated using lipid polymer membranes. The taste sensor can measure the taste perceived by humans and is called an electronic tongue with global selectivity, which is the property to discriminate taste qualities and quantify them without discriminating each chemical substance. This property is similar to the gustatory system; hence, the taste sensor is a type of biomimetic device. In this paper, we first explain the sensing mechanism of the taste sensor, its application to beer evaluation and the measurement mechanism. Second, the results recently obtained are introduced; i.e., the application of the sensor to high-potency sweeteners and the improvement of the bitterness sensor are explained. Last, the quantification of the bitterness-masking effect of high-potency sweeteners is explained using a regression analysis based on both the outputs of bitterness and sweetness sensors. The taste sensor provides a biomimetic method different from conventional analytical methods.

Keywords: taste sensor, lipid polymer membrane, bitterness-masking effect


Introduction

The sense of taste is one of the chemical senses and is of five basic types, namely, sourness, saltiness, sweetness, bitterness and umami. Umami is the fifth taste discovered by Ikeda in 1909. Only four basic tastes were recognized until the early 21st century. Umami was officially recognized worldwide as the fifth taste after the identification of the umami receptor in 2002, almost a century after umami was first discovered by Ikeda. The discovery of taste receptors began in the 21st century: bitterness taste receptors, Taste-2 receptors (T2Rs); sweetness receptors, T1R2+T1R3; and umami receptors, T1R1+T1R3. Although the mechanisms underlying the perception of sourness and saltiness have not yet been completely clarified, polycystic kidney disease 2-like 1 protein (PKD2L), acid-sensing ion channels (ASICs), hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, and epithelial sodium channels (ENaCs) have been proposed as the candidate receptors.

Astringency and pungency are not basic tastes but are recognized as tastes in a broad sense. These seven tastes are summarized in Table 1. Over the past 20 years, many researchers have provided evidence of free fatty acid receptors and the roles of G protein-coupled receptor 120 (GPR120), GPR40, and cluster of differentiation 36 (CD36) in the fat taste. In addition to the five basic tastes, the fat taste may be recognized as the sixth basic taste in the near future.

The sensory test is one of the main methods for taste assessment in food and pharmaceutical industries, in which well-trained panelists actually taste samples to evaluate their taste. Sensing technologies for the evaluation of food are being researched and developed for food and pharmaceutical industries because the sensory test has some problems, such as low objectivity and reproducibility as well as the stress it may impose on panelists.

Vlasov et al. defined, in an IUPAC Technical Report, that the “electronic tongue is a multisensory system, which consists of a number of low-selectivity sensors and uses advanced
mathematical procedures for signal processing based on the pattern recognition (PARC) and/or multivariate analysis...“12. The term “electronic tongue” was first introduced by Di Natale et al. in 199513. After that, Winquist and Lundström fabricated a voltammetric electronic tongue in 199714 and then developed a hybrid electronic tongue by combining potentiometric, voltammetric, and conductivity-based technologies15,16. Vlasov and coworkers applied solid-state crystalline ion-selective electrodes fabricated on chalcogenide glass to an electronic tongue17, and presented examples of applications of their system to the analysis and quality management of foods and beverages such as wine18 and mineral water by PCA and analysis using neural network techniques12. Wang et al. developed the voltammetric electronic tongue based on three nanocomposite-modified electrodes for identification of rice wines from different geographical origins19. Garcia-Hernandez et al. developed nanocomposites in an array, that is, the impedimetric electronic tongue, for discrimination of red wines by PCA and partial least squares regression-1 (PLS-1)20.

Suslick’s group developed paper-based colorimetric sensor arrays composed of multiple chemically responsive dyes for identification of the taste of beer, sweeteners and soft drinks21,22. Sehra et al. fabricated a dual shear horizontal surface acoustic wave (SH-SAW) device for the detection and identification of liquid by PCA23. Oliveira’s group developed a microfluidic electronic tongue24 and a paper-based electronic tongue for distinguishing types of sugar by capacitance measurements using carbon interdigitated electrodes coated with boronic acid-containing hydrogels25. Zribi et al. developed an amperometric sensory approach based on boron-doped diamond (BDD) electrodes with transition metal nanocatalysts for coffee discrimination26.

In the last few years, research on bioelectronic tongues consisting of a combination of biological tissues, (e.g., taste cells, the epithelium, and receptors)and sensor technologies, (e.g., potentiometry, voltammetry, impedance, optics and QCM) has been actively pursued27-31.
Toko et al. applied for a patent of their taste sensor in 1989 and developed a taste sensor equipped with multichannel electrodes using a lipid polymer membrane (hereafter lipid membrane) as the transducer before electronic tongues appeared. Toko and coworkers defined global selectivity as “the decomposition of the characteristics of a chemical substance into taste qualities and their quantification, rather than the discrimination of individual chemical substances, by mimicking the human tongue, on which the taste of foods is decomposed into individual types of taste by each taste receptor.” This concept is different from the selectivity of chemical sensor, biosensors, in which there is one-to-one correspondence to a particular chemical substance, and a device having this characteristic is called an electronic tongue with global selectivity. The electronic tongue with global selectivity, i.e., the taste sensor developed by Toko’s group, enabled the quantification of the five basic tastes and astringency, which are identified by the human tongue. It also successfully provided sensor outputs that are in good agreement with the results of sensory test conducted by panelists. Each sensor electrode with the lipid membrane of the taste sensor is not specific to a particular substance, which is similar to biological receptors in the gustatory system. As an example, Haraguchi et al. described that the taste sensor for the bitterness of drugs was highly sensitive to bitterness and correlated significantly with hT2R14. Recently, Peres’ group developed a potentiometric electronic tongue for the classification of olives using lipid membranes as the receptor. Sharma et al. also researched a lipid-polymer-based electronic tongue.

For taste evaluation, a taste sensing system was commercialized by Intelligent Sensor Technology, Inc., in 1993 as the world’s first commercialized electronic tongue system. Taste sensing systems with lipid membranes, i.e., SA402B and TS-5000Z, have been widely used in various fields, such as the food, beverage, and pharmaceutical industries, universities, and national research institutes. Currently, over 500 systems have been sold and are utilized in food and pharmaceutical companies throughout the world. The systems have applications in...
manufacturing of beverages and foodstuffs, such as rice, tea, wine, beer, pork, coffee, beef, kampo medicines formula, and active pharmaceutical ingredients. The taste sensor can be used in quantifying not only the taste of food but also the bitterness of medicines.

Nowadays, bitterness-masking is an important issue in the pharmaceuticals industry. Preis et al. reported the evaluation of the bitterness-masking effect of cyclodextrin using the taste sensor TS-5000Z. Uchida et al. evaluated orally disintegrating tablets (ODTs), which disintegrate easily in the mouth without water and are prescribed for the elderly, children and patients with poor swallowing ability, using TS-5000Z and OD-mate (Model IMC-14D1, Higuchi Inc., Tokyo, Japan), which is based on a disintegration test method.

Other commercialized sensors are Astree II manufactured by Alpha MOS, France, and Multiarray chemical sensor by McScience, Korea. These instruments help in market research, food control, and taste design for food and pharmaceuticals. The Astree II e-tongue system is used to discriminate solution samples using seven chemically sensitive field-effect transistor sensors, whereas the taste sensing systems SA402B and TS-5000Z are mainly used to quantify the intensity of each type of taste identified by the human tongue using a taste scale.

Aissy Inc., Japan, a university-originated venture from Keio University, provides taste analysis and services using multiple sensors. The technology information of their sensors is not public. Their system uses a neural network to analyze the optimization of ingredients to create a desired taste and investigate the relationship between trendy taste and commercial products.

A large number of publications have reported on the search for e-tongues. In this review, we focus on the taste sensor with lipid membranes, i.e. the electronic tongue with global selectivity. We describe the sensing concept and mechanism of the sensor, the characteristics of lipid membranes, and the applications of the sensor in pharmaceuticals and measurements of high-potency sweeteners and umami.
Principle of taste sensor

Table 2 shows a list of lipid membranes and their compositions, i.e., lipids, plasticizers, and polymer\(^6\), which affect the hydrophobicity and electrical charge of the membranes. The lipid membranes are coordinated for sensing each taste by changing the compounds and their concentrations. The taste felt by the human tongue, which is also the target of taste sensor, originates in the physicochemical attributes of a certain kind of substances. In accordance with the physicochemical properties of taste qualities shown in Figure 1, we designed the corresponding lipid membranes with different charge density and hydrophobicity conditions. For example, the bitterness sensor (C00) has a positively charged membrane surface with high hydrophobicity and was developed to allow an enhanced hydrophobic interaction with acidic bitter substances. While the sourness sensor (CA0) has an electrically neutral membrane surface with high hydrophilicity and was developed to detect protons produced by acids.

The chemical structures of lipids and plasticizers are shown in Figure 2. The lipids provide different charge densities of the membrane because they ionize in solution, causing the membrane to exhibit hydrophilicity. The plasticizers adjust the flexibility and interspace of the membrane. Both the lipids and plasticizers have relatively long carbon chains, which enhance the stability of the membrane components as well as adjust the hydrophobicity of the membrane. Taste substances interacting with a lipid membrane change the membrane potential, which is composed of the surface potential and the diffusion potential inside of the membrane. Changes in the membrane potential are measured using a potentiometer.

Fabrication of taste sensor using lipid membrane

A lipid membrane is fabricated as follows. First, a lipid is dissolved in tetrahydrofuran (THF). Next, a plasticizer is separately dissolved in THF, and then the two solutions are mixed. Next, poly-vinyl chloride (PVC) is added to the solution mixture. The solution mixture is placed on a Petri dish and allowed to evaporate to dryness at room temperature for 3 days. After THF is
evaporated, a membrane sample is obtained. The membrane sample is cut and attached to a sensor electrode, which has a Ag/AgCl electrode inside. The inside of the electrode is filled with saturated KCl solution. Finally, the sensor electrode is immersed in a standard solution (30 mM KCl and 0.3 mM tartaric acid in water) for 1 day before measurement for preconditioning. Figure 3 shows the schematic illustration of the resulting membrane structure. During the pretreatment process, the lipid molecules gradually moves towards the interface due to their hydrophilic groups.

Measurement procedure using taste sensor

The fabricated taste sensor electrodes and reference electrodes (Ag/AgCl electrode immersed in saturated KCl solution) are attached to a sensing system. Figure 4 shows the sensing system TS-5000Z, which has a sensing unit and an auto-sampling machine. The sensing unit measures voltage with a high impedance. There are two types of output of the measurement using the taste sensor, i.e., a relative value and a change in the membrane potential caused by adsorption (CPA) \(^{68,75-77}\). Due to different adsorption features of taste substances, these two measurement methods also contribute to distinguish different basic taste qualities by the change in membrane potential. The measurement is carried out as follows. First, the taste sensor electrodes and reference electrodes are immersed in the standard solution and the difference in electrical potential between the two electrodes is measured as \(V_r\). Next, the electrodes are immersed in a sample solution and the difference is measured as \(V_s\). Then, the electrodes are rinsed using another standard solution. After that, the electrodes are immersed in another standard solution and the difference is measured as \(V'_r\). The relative and CPA values are calculated as:

\[
\text{Relative value} = V_s - V_r, \quad (1)
\]
CPA value = $V_r' - V_r$.  

(2)

Finally, the electrodes are rinsed using a cleaning solution (100 mM KCl, 10 mM KOH for positively charged membranes or 10 mM HCl for negatively charged membranes, 30 vol% ethanol) and another standard solution. At least four measurements of each sample are performed. The average and standard deviation are calculated from the results, excluding those in the first measurement.

From the viewpoint of potential observation, the time required to the change on sensor membrane generated by taste substances is almost the same as that to the change on the membrane of taste receptor cells. However, the concept of the taste sensor aims to accurately and objectively quantify the first taste and after-taste that humans can perceive, rather than the response time. Therefore, the membrane potential measured within 30 seconds was used as the evaluation parameter for the consideration of potential stability.

Selectivity and sensitivity of taste sensors

Figure 5 shows the measurement results for sample solutions of the five basic tastes of various concentrations. Quinine, acetic acid, MSG, NaCl, and sucrose were used as samples of bitterness, sourness, umami, saltiness, and sweetness using the corresponding sensors, which were named BT0, CA0, AAE, CT0, and GL1, respectively. In the measurement of bitterness, the CPA value of the BT0 sensor was used as the output. The taste sensor can measure the concentration from human threshold to 10 times higher, which almost covers the concentration range in food fields. The thresholds of the sensor responses were almost the same as those of humans, who have very high sensitivity to bitterness and sourness because the substances related to the two tastes can be harmful to the human body. On the other hand, the sensitivity to sweetness was very low, similarly to humans who must eat sweet substances in large quantities,
as the source of energy to live. The concentration of lipids affects the sensitivity of sensor membrane. By adjusting the contents of lipids, the sensors with different sensitivity characteristics can be designed\cite{68}. In addition, the relationship between the concentration and the sensor responses was logarithmic. This relationship is the same as that in human sensation, which obeys Weber–Fechner’s law. The taste sensor has a better ability to distinguish the smallest detectable increment than the gustatory sense, which is about 20\%. According to Weber–Fechner’s law, sensor outputs can be linearly converted to “taste information,” which is information on taste quality defined by us based on each sensor characteristic.

Each sensor electrode is selective to each taste quality. For example, the BT0 sensor responds strongly to bitter substances such as quinine, cetirizine, hydroxyzine, and bromhexine but not to other taste solutions\cite{68}. The selectivity is not for each chemical substance but for the taste quality, as similarly observed for the gustatory system. We call this property “global selectivity”.

In addition, the output of each sensor electrode highly correlated with the results of the human sensory test. That is, the sensor output is large when the taste intensity felt by humans is high. In conclusion, the taste sensor with lipid membranes can evaluate the quality and intensity of each taste.

**Application to food evaluation**

The taste sensor is used to evaluate many types of food and drink products such as beer, wine, water, milk, sake, juice, soup, tea and coffee. Figure 6 shows a taste map of beer, which was made from the results of measurement using TS-5000Z. The horizontal axis is the strength of sourness, which is called the “dry taste”. The vertical axis is the strength of bitterness, which is called the “malt taste”. The origin point was plotted on the data point of Budweiser. The unit was set as follows. When the concentration difference between taste substances is larger than 20\%, humans can discriminate the difference. Thus, the difference was defined as 1 unit.
As can be seen from Fig. 3, Sapporo Yebisu (Japan), Bavaria (Netherlands), and Tsingtao (China) have a strong bitter taste. Carlsberg (Denmark) has a bitter taste. Holsten (B.R.D.), Budweiser (U.S.A.), and Hoegaarden White (Belgium) have a moderate taste with no bitterness. Asahi Super Dry (Japan), Heineken (Netherlands), Kronenbourg1664 (France) and Castlemaine XXXX (Australia) have a strong dry taste. The tastes can be understood visually if the taste sensor is used for the evaluation. This means that the taste sensor system can be a highly useful tool for the marketing of foods or development of new products.

Measurement mechanism of taste sensor and the surface structure

The taste sensor has selectivity to each taste quality and sensitivity that correlates with the human sensory test. These properties are controlled by changing the type and concentration of the lipid and plasticizer. The sensitivity is mainly affected by the concentration of charged lipids inside the membrane. When the lipid concentration is low, the surface potential can easily change even if the concentration of taste substances is low owing to the low surface charge density. Therefore, the membrane composed of low-density lipids shows high sensitivity to charged taste substances.

The selectivity is affected by both composition and species of lipids and plasticizers, which are mainly related to the hydrophobicity of the membrane surface. Generally speaking, the surface becomes hydrophilic when the concentration of lipids is high. In contrast, it becomes hydrophobic at high plasticizer concentrations. The selectivity is controlled by adjusting the composition carefully.

Another factor that can affect the properties is preconditioning, which is the process in which the sensor surface is immersed in a solution before use in measurements. In most cases, the membranes are immersed in a standard solution for one day before the measurement. The taste sensor C00, which is the bitterness sensor for negatively charged bitter substances, requires a
special preconditioning process different from those applied to other membranes\textsuperscript{78}. This special preconditioning involves the immersion of the taste sensor into the standard solution containing MSG (hereafter referred to as MSG preconditioning).

Figure 7 shows the changes in CPA values for iso-\(\alpha\)-acids and \(V_r\) of the C00 sensor with the MSG preconditioning, respectively\textsuperscript{79}. The C00 sensor containing TDAB is positively charged in the standard solution. Thus, \(V_r\) must be positive and the response to iso-\(\alpha\)-acids must be negative because the positively charged surface interacts with negatively charged bitter substances. The CPA value and \(V_r\) depended on the numbers of days of MSG preconditioning, which indicates that the surface charge density can be changed by the preconditioning process. The surface structure was analyzed to reveal the changes in the surface charge density induced by MSG preconditioning.

First, the contact angle of the surface was measured to evaluate the hydrophobicity of the surface. The contact angle decreased monotonically from an initial value of 87° to 80°, 75°, 68°, and 61° after 6, 7, 8, and 9 days of MSG preconditioning, respectively\textsuperscript{79}. This result indicates that the surface became gradually hydrophilic during the MSG preconditioning. Lipid molecules such as TDAB and umami substances such as MSG may be responsible for the hydrophilicity because they can be ionized in the aqueous phase. We have carried out two chemical analyses\textsuperscript{79}: X-ray photon spectroscopy (XPS) and gas cluster ion beam-time of flight-secondary ion mass spectrometry (GCIB-TOF-SIMS).

XPS provides information of not only the types of atom but also the chemical conditions of atoms from the surface to a depth of about 2 nm. Figure 8 shows the result of XPS where the measured samples are indicated by symbols with three numbers. The first and second numbers are the amounts of TDAB and NPOE, respectively. The third number is the number of the days of MSG preconditioning. For example, sample 1-1-7 is the normal C00 sensor. Sample 100-1-7 contains more 100 times TDAB than the C00 sensor. Sample 0-0-0 has a membrane containing
PVC only. The left graph is a plot of the results of a wide scan showing the signals of oxygen, carbon, chlorine, and nitrogen. The right graph shows the results of a narrow scan of nitrogen signals.

In the samples without MSG preconditioning, no nitrogen signals were observed except for sample 1000-0-0. The compounds containing nitrogen are MSG, TDAB, and NPOE. The absence of nitrogen signals means that the concentrations of these compounds in the surface region were below 1% in the samples without MSG preconditioning. In addition, the peak at 402 eV corresponds to the signal of TDAB because TDAB was present in sample 1000-0-0 only. On the other hand, there were two peaks at 400 and 402 eV in the samples with MSG preconditioning. This means that the compounds containing nitrogen were concentrated in the surface region by MSG preconditioning. The result for sample 0-0-7 suggests that the peak at 400 eV corresponded to the signal of MSG because the sample 0-0-7 did not contain TDAB or NPOE. The results for samples 1-1-7 and 100-1-7 show two peaks suggesting that TDAB and MSG in the surface region were concentrated by MSG preconditioning. In conclusion, MSG preconditioning might provide two effects: the adsorption of MSG onto the surface followed by diffusion into the membrane, and the concentration of TDAB in the surface region.

Second, the depth profiles of the concentrations of the components of the C00 sensor were evaluated by GCIB-TOF-SIMS to support the results of XPS measurements. The concentrations of TDAB and MSG in the surface region after MSG preconditioning were higher than those before the process. This observation also indicates that TDAB concentrated in the surface region and MSG diffused from the surface to the bulk region of the membrane. This result supports the finding of contact angle measurement that TDAB and MSG can be ionized and cause hydrophilicity of the surface. In addition, these results are also in agreement with the CPA value and \( V \), shown in Fig. 4. The surface was charged more positively because positively charged TDAB can be concentrated on the surface by MSG preconditioning. The more
positively charged surface provides a higher CPA value to iso-α-acids. In conclusion, the concentrations of TDAB and MSG were increased by MSG preconditioning, and the surface potential became more positively charged because of the higher concentration of TDAB.

**Taste sensor for high-potency sweeteners**

Sweetener molecules are mainly received by the heterodimeric receptor T1R2 + T1R3 on taste cells. Sweeteners are classified into natural sugars, sugar alcohols, sweet-tasting proteins, and high-potency sweeteners (natural or artificial). There are some methods for the evaluation of sweetness, such as the Brix and NIR or FT-IR methods. These methods mainly estimate the quantities of uncharged sweeteners. As shown in Fig. 2, the taste sensor GL1 can quantify the sweetness of uncharged sweeteners such as sucrose and fructose.

As health-oriented concerns have increased worldwide, research and development of low-calorie foods and beverages are being actively promoted in food industries. High-potency sweeteners are utilized to reduce the consumption of table sugar. The number of times that a sweetener is sweeter than sucrose is called sweetener potency. The potency of a sweetener is compared with sucrose mainly in terms of the threshold levels of the sweetener and sucrose. Sweeteners that have a sweetener potency exceeding 10 are called high-potency sweeteners. In beverages and foods, a mixture of multiple high-potency sweeteners are often used, and the concentrations of sweeteners in drink samples on the market are as follows: saccharin sodium 0.15 to 0.4 mM; acesulfame potassium 0.2 to 0.7 mM; aspartame 0.1 to 1.3 mM. We have developed taste-sensing lipid membranes for the most prevalent high-potency sweeteners which can be used in this target concentration ranges.

**Taste sensor for negatively charged high-potency sweeteners**

A positively charged lipid, TDAB, was used in a lipid membrane consisting of NPOE for
negatively charged high-potency sweeteners, saccharin sodium, and acesulfame potassium. Figure 10 shows the CPA values for various kinds of taste substances measured using the membrane containing 30 mg of TDAB. This figure shows that the sensor has high selectivity to saccharin sodium and acesulfame potassium. Moreover, the CPA values increased with increasing concentrations of saccharin sodium and acesulfame potassium, whereas the detection limits (blank ± 3SD) were 0.028 and 0.024 mM, respectively. The fabricated taste sensor for negatively charged high-potency sweeteners had satisfactory performance as a prototype model.

Taste sensor for positively charged high-potency sweetener

A negatively charged lipid, PADE, was used in a lipid membrane for positively charged high-potency sweeteners, aspartame. Hydrophobic adsorption of aspartame to lipid membranes can be expected, because aspartame is a dipeptide obtained by formal condensation of the alpha-carboxy group of l-aspartic acid with the amino group of methyl l-phenylalaninate, which has hydrophobicity. Eight plasticizers, phosphoric acid tris(2-ethylhexyl) ester (PTEH), trioctyl trimelitate (TOTM), tributyl O-acetylcitrate (TBAC), bis(1-butylpentyI) adipate (BBPA), diethylene glycol dibutyl ether (DGDE), dioctyl phenyl phosphonate (DOPP), nitrophenyl n-octyl ether (NPOE), and 2-butoxyethyl oleate (BEO), are candidates for actual use. The lipid PADE is negatively charged; hence, quinine hydrochloride, a bitter hydrophobic substance, is an interfering substance. The sensor response was below 5 mV in the case of using PTEH, DOPP, and OGDE as plasticizers. The response to quinine exceeded 10 mV when TBAC, BBPA, TOTM, and NPOE were used as plasticizers. Among the plasticizers used in the experiment, BEO was found to be the most suitable in terms of the sensitivity and selectivity of the sensor response. Figure 11 shows the concentration dependence of CPA values for aspartame when using PADE, BEO, and PVC as the membrane. The CPA values indicated good sensitivity and
selectivity to aspartame and the fabricated taste sensor for aspartame had satisfactory performance as a prototype model.

Stevioside is a white crystalline compound of Stevia rebaudiana leaf, which is widely known for its sweetness intensity (100–300 times sweeter than sucrose)\textsuperscript{92}. Since it is non-caloric and natural, stevioside has attracted much attention and high demand especially for diabetic, Phenylketonuria and obesity patients in several countries\textsuperscript{93}. However, the detection of stevioside using the conventional potential theory is difficult because it is uncharged. In the future, realization of a sensor for stevioside is desired.

**Bitterness sensor and bitterness-masking effect**

The bitterness sensor (BT0) is one of the sensor electrodes for bitterness quantification of hydrochloride salts, such as quinine hydrochloride, hydroxyzine chloride, and bromhexine hydrochloride. Because hydrochloride salts are often used as active ingredients in pharmaceuticals, the BT0 sensor has so far been used to evaluate the bitterness of pharmaceuticals\textsuperscript{94,95}. In this section, the bitterness is evaluated using the BT0 sensor.

**Elucidation of mechanism of response deterioration of bitterness sensor**

The membrane of the BT0 sensor contains phosphoric acid di-n-decyl ester (PADE) as the lipid, bis(1-butylpentyl) adipate (BBPA) and tributyl o-acetylctirate (TBAC) as the plasticizers\textsuperscript{55}, as shown in Table 2. In a previous study, the BT0 sensor showed a high selectivity to bitterness and good correlation with human sensory test results\textsuperscript{39,55}. However, the sensor response decreases to half after one year of storage at room temperature and normal humidity. To clarify the reason behind response deterioration and enhancement of sensor durability, we investigated the changes in the membrane state and response before and after the deterioration process. The deterioration process simulates the deterioration of one year in one month by increasing the
ambient temperature and humidity.

Figure 12 shows the sensor responses with the contents of lipid PADE before and after the deterioration process\(^9\). 100% PADE means the amount of PADE in the conventional BT0 sensor. Before the deterioration, the sensor response keeps increasing when the concentration of lipid PADE is below 90% and then remains unchanged when it is over 90%. After the deterioration process, the sensor response increased initially and then decreased with the PADE concentration when the PADE concentration was over 90%. When the PADE concentration is less than 33%, the deterioration of response was nominal, which indicates that the amount of PADE is a key factor for response deterioration.

To clarify the change in the substances in the membrane before and after the deterioration of response, liquid chromatography–tandem mass spectrometry (LC-MS/MS) was adopted to compare the differences in the amounts of PADE, TBAC and BBPA in the membrane before and after deterioration. As a result, only the amount of TBAC was significantly reduced after the deterioration of response, whereas the amounts of PADE and BBAC did not change\(^9\). Moreover, butyl citrate as the acidic hydrolysis product of TBAC, clearly increased after the deterioration of response, as determined from the result of gas chromatography-mass spectrometry (GC-MS)\(^9\).

These results suggest that the phosphoric acid PADE provides protons in the membrane environment and promotes the hydrolysis of TBAC. During the long-term storage, the hydrolysate of TBAC produced butyl citrate after the deterioration of response, as explained below. It was found that the reference potential \(V_r\) decreased irrespective of the PADE concentration after the deterioration of response. This means that negatively charged substances were generated after the deterioration because of the decomposition of TBAC and the generation of negatively charged acetic acid and increased the surface charge density of the membrane. On the other hand, the amount of quinine hydrochloride adsorbed to the sensor
membrane was the same before and after the deterioration\textsuperscript{96}. The reason for the decrease in CPA value is the same as we reported in a previous study\textsuperscript{97}, the CPA value is affected by two factors—surface charge density and amount of adsorbed iso-\(\alpha\)-acids. The decrease in CPA value despite the constant amount of adsorbed iso-\(\alpha\)-acids is caused by the decrease in the sensitivity of the membrane as the surface charge density increases.

\textit{Three categories of bitterness-masking effect}

The bitterness-masking effect can be classified into three categories on the basis of the mechanism of the effect: physical masking, biochemical masking and functional masking. The physical masking effect includes the use of capsules for bitter drugs as well as orally disintegrating tablets to which masking particles made of different gastric-soluble coating are added\textsuperscript{98}. The biochemical masking effect involves the use of a chemical modification method by, for example, allowing prodrugs or cyclodextrin to interact with a bitter material by inclusion\textsuperscript{99}. Functional masking, sometimes called organoleptic masking, means the balancing of corresponding substances released in the brain when tasting bitterness and another taste quality such as sweetness or sourness simultaneously\textsuperscript{100}. Taking into account the position where the effect occurs, we can assign the physical masking and biochemical masking to the masking effect occurring on the tongue, and the functional masking to the masking effect occurring in the brain.

\textit{Quantification of bitterness-masking effect on the tongue}

As shown in Fig. 2, the taste sensor for basic bitterness can measure bitterness as CPA values corresponding to the after-taste felt by humans caused by membrane potential changes due to bitter substances adsorbed onto the lipid membrane\textsuperscript{75,97,101}. By applying this phenomenon, the sensor can evaluate the effect of hydrophobic bitterness-masking substances that can mask bitter
receptors directly. In this section, we introduce a method of evaluating bitterness-masking substances. A commercialized bitterness-masking substance, BMI-40, consisting of lipoprotein composed of phosphatidic acid (PA) and β-lactoglobulin (LG)\textsuperscript{102,103} has been used as a food additive (Kao Co., Ltd., Japan.).

The amount of quinine hydrochloride adsorbed onto the lipid membrane was measured as follows\textsuperscript{104}: 5 ml of quinine hydrochloride was dropped onto a Petri dish on which the lipid membrane consisting of PADE, BBPA, TBAC, and PVC was formed, and the membrane is immersed in the quinine hydrochloride solution for 30 s. Then, 3 ml of the quinine hydrochloride solution was removed from the Petri dish and absorbance was measured using a UV spectrophotometer. The quinine hydrochloride concentration was determined using the measured absorbance and the calibration curve. The difference between the concentration of the dropped quinine hydrochloride solution and the concentration of quinine hydrochloride removed was taken as the amount of adsorbed quinine hydrochloride.

When the concentrations of quinine hydrochloride dropped were 0.01, 0.1, 0.03, 0.1, 0.3, and 1 mM, the adsorbed amounts and CPA values were approximately 0.26, 0.48, 0.76, 20.5, and 7.3 \(\mu\)g/cm\(^2\) and approximately 5, 15, 43, 70, and 95 mV, respectively. When 0.7% BMI-40 was mixed with 0.3 mM quinine solution, the amount of quinine adsorbed onto the membrane was reduced by 63\%, which indicates that the lipid membrane can be applied to the performance evaluation of bitterness-masking substances. Moreover, when BMI-40 was added to quinine solutions, both the sensory scores and CPA values decreased with increasing amount of BMI-40 added\textsuperscript{55}. According to a previous study\textsuperscript{55}, both the suppression effect of binding and neutralizing bitter substances in aqueous solutions and of covering the sensor membrane by bitterness-masking materials were considered to contribute to the suppression of bitterness. Therefore, it was shown that the sensor for basic bitterness can be applied to the evaluation of bitterness-masking substances that suppress bitterness by directly masking bitter taste receptors.
Quantification of bitterness-masking effect in the brain

As mentioned above, a conventional bitterness sensor can not only detect the bitterness suppression interaction between bitterness-masking substances and bitter substances but also express the suppression effect caused by the covering of the tongue surface (i.e., sensor membrane)\(^6\). However, the bitterness-masking effect in the brain caused by flavors or sweeteners cannot be detected by using only the bitterness sensor. To quantitatively express the taste interactions perceived by humans, we proposed a method of imitating the pathway of taste perception by replacing the taste detected by different taste receptors with different taste sensors, which have real taste meanings. Each sensor responds to a class of substances with the same taste quality, which is similar to the function of human taste receptors. A previous research\(^1^0^5\) focused on the responses of bitterness and sweetness sensors to mixed solutions consisting of quinine hydrochloride and high-potency sweeteners (aspartame or saccharine sodium).

The response of the bitterness sensor is proportional to the logarithm of the concentration of quinine hydrochloride and is unaffected by the concentration of high-potency sweeteners. The sweetness sensors have similar selectivity to aspartame and saccharine sodium. That is, the sensors of these two substances have relatively independent selectivity just like the selective function of taste receptors. To reproduce the method by which the human brain analyzes taste signals from different receptors, we proposed estimation formulas for evaluating the bitterness-masking effect of high-potency sweeteners by regression analysis, using the outputs of the bitterness and sweetness sensors.

The bitterness of standard solutions of quinine hydrochloride was evaluated using the bitterness sensor. The suppression of bitterness was converted from the sweetness scores measured using the taste sensors of high-potency sweeteners, as expressed by the second term of Eq. (3). The CPA values of these sensors were used in the data analysis, and the model for
estimating bitterness is represented as

\[ Y = Y_{\text{bitter}} - kY_{\text{sweet}} + m, \]  

(3)

where \( Y \) is the bitterness score of each sample and \( Y_{\text{bitter}} \) is the bitterness score of quinine hydrochloride of each sample. \( Y_{\text{sweet}} \) is the sweetness score of high-potency sweeteners present in each sample. This formula is very simple and intuitive, and therefore easy to understand.

Figure 13 shows the relationship between the estimated bitterness and the bitterness sensory score obtained from the estimating formulas\(^{105}\). The estimated bitterness showed good correlation with human taste. Moreover, the standard deviation of human taste was larger than that of the estimated bitterness, which indicates the superior performance of the taste sensor in quantifying taste information compared with the sensory test.

**Conclusions (optional)**

In this review, an electronic tongue with lipid membranes has been introduced. It is also named the taste sensor because of the sensory consistency in human gustatory system, which is called global selectivity. We tried to analyze the structure of the membrane surface using optical methods to better understand the response mechanism, which may provide more ideas for membrane design in the future. In addition, a new psychochemical modification (preconditioning) is considered to let the membrane respond to uncharged taste substances.

As the population decline and population aging have become global issues, a happy and safe society with improved social services attracts more and more concerns. In future, the digitization of taste will promote the standardization of taste expression and the establishment of personalized taste database, with the development of the Internet of Things (IOT) and artificial intelligence (AI). The application will have broad market prospects, not only limited to conventional foods or beverages, but also extended to the diets of elderly, taste disorders (e.g.
hospital diets for patients) as well as the situation that sensory test cannot be carried out easily (e.g. drugs and pet food).

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Figure Captions

Fig. 1  Physicochemical properties of the five basic taste qualities.

Fig. 2  Chemical structures of lipids and plasticizers.

Fig. 3  Schematic illustration of the resulting membrane structure.

Fig. 4  Taste sensing system TS-5000Z.

Fig. 5  Concentration dependence of five types of sensor for the five basic tastes\(^{53}\).

Fig. 6  Taste map of beers.

Fig. 7  Electrode potential \(V_r\) and CPA value dependence on number of days of MSG preconditioning\(^{79}\).

Fig. 8  Results of XPS measurements. The left graph shows the result of wide scan. The right graph shows the result of narrow scan of nitrogen signals (396 – 404 eV)\(^{79}\).

Fig. 9  Chemical structures of sweeteners. (a) Uncharged sweeteners. (b) Negatively charged high-potency sweeteners. (c) Positively charged high-potency sweeteners.

Fig. 10  CPA values of other taste substances.

Fig. 11  Concentration dependence of CPA values of aspartame on the membrane comprising of PAEE, BEO, and PVC.

Fig. 12  Relationship between sensor response and lipid concentration before and after
deterioration of response. 100% PADE means the amount of PADE in the conventional BT0 sensor. The results are expressed as the mean ± SD (n = 4)\(^{36}\).

Fig. 13 Relationship between bitterness estimated using taste sensor and bitterness scores from sensory test of mixture of quinine hydrochloride and aspartame\(^{105}\).

Table 1 Main materials and features of seven taste qualities.

Table 2 Chemical components of each taste sensor.

References

1. K. Ikeda, *Chem. Senses*, **2002**, 27, 847.
2. G. Nelson, J. Chandrashekar, M. A. Hoon, L. Feng, G. Zhao, N. J. P. Ryba, and C. S. Zuker, *Nature*, **2002**, 416, 199.
3. D. Gaillard and S. C. Kinnamon, *Acta Physiol.*, **2019**, 226, e13246.
4. J. Chandrashekar, K. L. Mueller, M. A. Hoon, E. Adler, L. Feng, W. Guo, C. S. Zuker, and N. J. P. Ryba, *Cell*, **2000**, 100, 703.
5. G. Nelson, M. A. Hoon, J. Chandrashekar, Y. Zhang, N. J. P. Ryba, and C. S. Zuker, *Cell*, **2001**, 106, 381.
6. C. Montell, *Science*, **2018**, 359, 991.
7. A. L. Huang, X. Chen, M. A. Hoon, J. Chandrashekar, W. Guo, D. Trankner, N. J. P. Ryba, and C. S. Zuker, *Nature*, **2006**, 442, 934.
8. J. Chandrashekar, C. Kuhn, Y. Oka, D. A. Yarmolinsky, E. Hummler, N. J. P. Ryba, and C. S. Zuker, *Nature*, **2010**, 464, 297.
9. L. J. Falomir-Lockhart, G. F. Cavazzutti, E. Giménez, and A. M. Toscani, *Front. Cell. Neurosci.*, **2019**, 13.
10. K. Yasumatsu, S. Iwata, M. Inoue, and Y. Ninomiya, *Acta Physiol.*, **2019**, 226, e13215.
11. S.-J. Lee, I. Depoortere, and H. Hatt, *Nat. Rev. Drug Discov.*, 2019, 18, 116.

12. Y. Vlasov, A. Legin, A. Rudnitskaya, C. Di Natale, and A. D’Amico, *Pure Appl. Chem.*, 2005, 77, 1965.

13. C. Di Natale, A. D’amico, Y. G. Vlasov, A. V Legin, and A. M. Rudnitskaya, *Proc. Intern. Conf. EUROSENSORS IX*, 1995, 36.

14. F. Winquist, P. Wide, and I. Lundström, *Anal. Chim. Acta*, 1997, 357, 21.

15. F. Winquist, *Microchim. Acta*, 2008, 163, 3.

16. F. Winquist, I. Lundström, and P. Wide, *Sens. Actuators B Chem.*, 1999, 58, 512.

17. Y. G. Vlasov, E. A. Bychkov, and A. V Legin, *Talanta*, 1994, 41, 1059.

18. A. Legin, A. Rudnitskaya, Y. Vlasov, C. Di Natale, F. Davide, and A. D’Amico, *Sensors Actuators B Chem.*, 1997, 44, 291.

19. J. Wang, L. Zhu, W. Zhang, and Z. Wei, *Anal Chim Acta*, 2019, 1050, 60.

20. C. Garcia-Hernandez, C. Salvo Comino, F. Martín-Pedrosa, M. L. Rodriguez-Mendez, and C. Garcia-Cabezon, *Sensors Actuators B Chem.*, 2018, 277, 365.

21. C. J. Musto, S. H. Lim, and K. S. Suslick, *Anal. Chem.*, 2009, 81, 6526.

22. C. Zhang and K. S. Suslick, *J. Am. Chem. Soc.*, 2005, 127, 11548.

23. G. Sehra, M. Cole, and J. W. Gardner, *Sensors Actuators B Chem.*, 2004, 103, 233.

24. C. M. Daikuzono, C. A. R. Dantas, D. Volpati, C. J. L. Constantino, M. H. O. Piazzetta, A. L. Gobbi, D. M. Taylor, O. N. Oliveira, and A. Riul, *Sensors Actuators B Chem.*, 2015, 207, 1129.

25. C. M. Daikuzono, C. Delaney, A. Morrin, D. Diamond, L. Florea, and O. N. Oliveira, *Analyst*, 2019, 144, 2827.

26. B. Zribi, D. Dragoe, and E. Scorsone, *Sensors Actuators B Chem.*, 2019, 290, 147.

27. J. S. Lee, A.-N. Cho, Y. Jin, J. Kim, S. Kim, and S.-W. Cho, *Biomaterials*, 2018, 151, 24.
28. H. S. Song, H. J. Jin, S. R. Ahn, D. Kim, S. H. Lee, U.-K. Kim, C. T. Simons, S. Hong, and T. H. Park, *ACS Nano*, 2014, 8, 9781.
29. P. Chen, X. Liu, B. Wang, G. Cheng, and P. Wang, *Sensors Actuators B Chem.*, 2009, 139, 576.
30. Q. Liu, F. Zhang, D. Zhang, N. Hu, H. Wang, K. Jimmy Hsia, and P. Wang, *Biosens. Bioelectron.*, 2013, 40, 115.
31. S. R. Ahn, J. H. An, I. H. Jang, W. Na, H. Yang, K. H. Cho, S. H. Lee, H. S. Song, J. Jang, and T. H. Park, *Biosens. Bioelectron.*, 2018, 117, 628.
32. K. Hayashi, M. Yamanaka, K. Toko, and K. Yamafuji, *Sens. Actuators B Chem.*, 1990, 2, 205.
33. K. Toko, *Mater. Sci. Eng. C*, 1996, 4, 69.
34. Y. Tahara and K. Toko, *IEEE Sens. J.*, 2013, 13, 3001.
35. K. Toko, T. Onodera, and Y. Tahara, “Bio-Nanotechnology: A Revolution in Food, Biomedical and Health Sciences”, eds. D. Bagchi, M. Bagchi, H. Moriyama, and F. Shahidi, 2013, Blackwell Publishing Ltd., 270.
36. K. Toko, Y. Tahara, M. Habara, Y. Kobayashi, and H. Ikezaki, “Essentials of Machine Olfaction and Taste”, ed. T. Nakamoto, 2016, Chap. 4, WILEY, 87.
37. V. Anand, M. Kataria, V. Kukkar, V. Saharan, and P. K. Choudhury, *Drug Discov. Today*, 2007, 12, 257.
38. A. Riul Jr, C. A. R. Dantas, C. M. Miyazaki, and O. N. Oliveira Jr, *Analyst*, 2010, 135, 2481.
39. T. Haraguchi, T. Uchida, M. Yoshida, H. Kojima, M. Habara, and H. Ikezaki, *Chem. Pharm. Bull.*, 2018, 66, 71.
40. L. G. Dias, A. Fernandes, A. C. A. Veloso, A. A. S. C. Machado, J. A. Pereira, and A. M. Peres, *Food Chem.*, 2014, 160, 321.
41. Í. Marx, N. Rodrigues, L. G. Dias, A. C. A. Veloso, J. A. Pereira, D. A. Drunkler, and A. M. Peres, *Talanta*, 2017, 162, 98.

42. Í. M. G. Marx, N. Rodrigues, L. G. Dias, A. C. A. Veloso, J. A. Pereira, D. A. Drunkler, and A. M. Peres, *LWT - Food Sci. Technol.*, 2017, 79, 394.

43. G. Sharma, S. Kumar, A. Kumar, A. Sharma, R. Kumar, R. Kaur, and A. P. Bhondekar, *Procedia Comput. Sci.*, 2015, 70, 146.

44. P. Ciosek and W. Wróblewski, *Analyst*, 2007, 132, 963.

45. T. U. Tran, K. Suzuki, H. Okadome, S. Homma, and K. Ohtsubo, *Food Chem.*, 2004, 88, 557.

46. N. Hayashi, T. Ujihara, R. Chen, K. Irie, and H. Ikezaki, *Food Res. Int.*, 2013, 53, 816.

47. A. Totsuka, “Biochemical Sensors: Mimicking Gustatory and Olfactory Senses”, ed. K. Toko, 2013, Pan Stanford Publishing.

48. K. Toko and Y. Tahara, “Electronic Noses and Tongues in Food Science”, ed. Maria Luz Rodriguez Mendez, 2016, Chap. 16, Oxford: Academic Press, 161.

49. K. Sasaki, F. Tani, K. Sato, H. Ikezaki, A. Taniguchi, T. Emori, F. Iwaki, K. Chikuni, and M. Mitsumoto, *Sensors Mater.*, 2005, 17, 397.

50. Y. H. Hwang, I. Ismail, and S. T. Joo, *Korean J. Food Sci. Anim. Resour.*, 2018, 38, 1305.

51. T. Ishiwaki, “Biochemical Sensors: Mimicking Gustatory and Olfactory Senses”, ed. K. Toko, 2013, Pan Stanford Publishing, 83.

52. X. Zhang, Y. Zhang, Q. Meng, N. Li, and L. Ren, *PLoS One*, 2015, 10, e0137807.

53. N. Anjiki, J. Hosoe, H. Fuchino, F. Kiuchi, S. Sekita, H. Ikezaki, M. Mikage, N. Kawahara, and Y. Goda, *J. Nat. Med.*, 2011, 65, 293.

54. M. Guhmann, M. Preis, F. Gerber, N. Pöllinger, J. Breitkreutz, and W. Weitschies, *Int. J. Pharm.*, 2012, 438, 81.
55. Y. Kobayashi, H. Hamada, Y. Yamaguchi, H. Ikezaki, and K. Toko, *IEEJ Trans. Electron. Eng.*, **2009**, *4*, 710.

56. T. Harada, T. Uchida, M. Yoshida, Y. Kobayashi, R. Narazaki, and T. Ohwaki, *Chem. Pharm. Bull.*, **2010**, *58*, 1009.

57. M. Okamoto, H. Sunada, M. Nakano, and R. Nishiyama, *Asian J. Pharm. Sci.*, **2009**, *4*, 1.

58. M. Pein, M. Preis, C. Eckert, and F. E. Kiene, *Int. J. Pharm.*, **2014**, *465*, 239.

59. M. Preis, L. Grother, P. Axe, and J. Breitkreutz, *Int. J. Pharm.*, **2015**, *491*, 8.

60. T. Uchida, M. Yoshida, M. Hazekawa, T. Haraguchi, H. Furuno, M. Teraoka, and H. Ikezaki, *J. Pharm. Pharmacol.*, **2013**, *65*, 1312.

61. Y. Bi, H. Sunada, Y. Yonezawa, K. Danjo, A. Otsuka, and K. Iida, *Chem. Pharm. Bull.*, **1996**, *44*, 2121.

62. R. Kakutani, H. Muro, and T. Makino, *Chem. Pharm. Bull.*, **2010**, *58*, 885.

63. K. Woertz, C. Tissen, P. Kleinebudde, and J. Breitkreutz, *J. Pharm. Biomed. Anal.*, **2011**, *55*, 272.

64. G. A. Campbell, J. A. Charles, K. Roberts-Skilton, M. Tsundupalli, C. K. Oh, A. Weinecke, R. Wagner, and D. Franz, *Powder Technol.*, **2012**, *224*, 109.

65. X. Tian, J. Wang, R. Shen, Z. Ma, and M. Li, *Int. J. Food Sci. Technol.*, **2019**, *54*, 670.

66. J. Do Kim, H. G. Byun, D. J. Kim, Y. K. Ham, W. S. Jung, and C. O. Yoon, *Talanta*, **2006**, *70*, 546.

67. K. Woertz, C. Tissen, P. Kleinebudde, and J. Breitkreutz, *Int. J. Pharm.*, **2011**, *417*, 256.

68. Y. Kobayashi, M. Habara, H. Ikezaki, R. Chen, Y. Naito, and K. Toko, *Sensors*, **2010**, *10*, 3411.

69. A. Inc., No Title, [https://aissy.co.jp/](https://aissy.co.jp/)

70. M. del Valle, *Int. J. Electrochem.*, **2012**, *2012*, 11.
71. K. Toko, “Biomimetic Sensor Technology”, 2000, Cambridge University Press.

72. Y. G. Vlasov, A. V Legin, and A. M. Rudnitskaya, Russ. J. Gen. Chem., 2008, 78, 2532.

73. L. Escuder-Gilabert and M. Peris, Anal. Chim. Acta, 2010, 665, 15.

74. T. Haraguchi, M. Yoshida, H. Kojima, and T. Uchida, Asian J. Pharm. Sci., 2016, 11, 479.

75. H. Ikezaki, A. Taniguchi, and K. Toko, IEEJ Trans. Sensors Micromachines, 1997, 117, 465.

76. M. Habara and K. Toko, “Encyclopedia of Sensors”, 2006, Vol. 10, American Scientific Publishers, 107.

77. M. Habara and K. Toko, “Bottom-Up Nanofabrication”, ed. Katsuhiko Ariga and Singh Nalwa Hari, 2009, Vol. 6, American Scientific Publishers, 91.

78. I. Insent, Rep. Risk-taking Fund Technol. Dev., 2007, 25.

79. R. Yatabe, J. Noda, Y. Tahara, Y. Naito, H. Ikezaki, and K. Toko, Sensors, 2015, 15, 22439.

80. C. Belloir, F. Neiers, and L. Briand, Curr Opin Clin Nutr Metab Care, 2017, 20, 279.

81. K. Toyota, H. Cui, K. Abe, M. Habara, K. Toko, and H. Ikezaki, Sensors Mater., 2011, 23, 465.

82. K. Toyota, H. Cui, K. Abe, M. Habara, K. Toko, and H. Ikezaki, Sensors Mater., 2011, 23, 475.

83. M. Yasuura, Q. Shen, Y. Tahara, R. Yatabe, and K. Toko, Sensors Mater., 2015, 27, 351.

84. N. A. Miele, E. K. Cabisidan, A. Galiñanes Plaza, P. Masi, S. Cavella, and R. Di Monaco, Trends Food Sci. Technol., 2017, 64, 87.

85. R. Di Monaco, N. A. Miele, E. K. Cabisidan, and S. Cavella, Curr. Opin. Food Sci., 2018, 19, 92.

29
86. A. D. Mooradian, M. Smith, and M. Tokuda, *Clin Nutr ESPEN*, **2017**, *18*, 1.

87. B. Sik, *Food Anal. Methods*, **2012**, *5*, 1443.

88. M. Yasuura, H. Okazaki, Y. Tahara, H. Ikezaki, and K. Toko, *Sensors Actuators B Chem.*, **2014**, *201*, 329.

89. M. Yasuura, Y. Tahara, H. Ikezaki, and K. Toko, *Sensors*, **2014**, *14*, 7359.

90. Y. Tahara, T. Hattori, X. Wu, R. Yatabe, H. Ikezaki, M. Habara, and K. Toko, in 2017 ISOCS/IEEE International Symposium on Olfaction and Electronic Nose (ISOEN), **2017**, Montreal, 265–266.

91. H. Okazaki, M. Yasuura, Y. Tahara, H. Ikezaki, and K. Toko, *Japanese J. Tast. Smell Res.*, **2014**, *21*, 395.

92. S. K. Goyal, Samsher, and R. K. Goyal, *Int. J. Food Sci. Nutr.*, **2010**, *61*, 1.

93. V. Chatsudthipong and C. Muanprasat, *Pharmacol. Ther.*, **2009**, *121*, 41.

94. T. Harada, T. Uchida, M. Yoshida, Y. Kobayashi, R. Narazaki, and T. Ohwaki, *Chem. Pharm. Bull.*, **2010**, *58*, 1009.

95. T. Haraguchi, T. Uchida, M. Yoshida, H. Kojima, M. Habara, and H. Ikezaki, *Chem. Pharm. Bull.*, **2018**, *66*, 71.

96. X. Wu, H. Onitake, Z. Huang, T. Shiino, Y. Tahara, R. Yatabe, H. Ikezaki, and K. Toko, *Sensors*, **2017**, *17*.

97. K. Toko, D. Hara, Y. Tahara, M. Yasuura, and H. Ikezaki, *Sensors*, **2014**, *14*, 16274.

98. T. Sugiiura, S. Uchida, and N. Namiki, *Chem. Pharm. Bull.*, **2012**, *60*, 315.

99. V. Sharma and H. Chopra, *Int. J. Pharm. Pharm. Sci.*, **2010**, *2*, 14.

100. S. S. Schiffman, S. Consulting, and H. Place, *Chem Senses.*, **2012**, *37*, 671.

101. Y. Harada, Y. Tahara, and K. Toko, *Sensors*, **2015**, *15*, 6241.

102. Y. Katsuragi, T. Yasumatsu, and K. Kurihara, *Brain Res.*, **1996**, *713*, 240.

103. Y. Katsuragi and K. Kurihara, *Nature*, **1993**, *365*, 213.
104. T. Fukagawa, Y. Tahara, M. Yasuura, M. Habara, H. Ikezaki, and K. Toko, *J. Innov. Electron. Commun.*, 2012, 2, 1.

105. X. Wu, H. Onitake, T. Haraguchi, Y. Tahara, R. Yatabe, M. Yoshida, T. Uchida, H. Ikezaki, and K. Toko, *Sensors Actuators, B Chem.*, 2016, 235, 11.

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Figure 13 The relationship between the estimated bitterness using taste sensor and the bitterness scores from sensory test in the mixture of quinine hydrochloride and aspartame.^6^
| Taste   | Main materials                                      | Feature                              |
|---------|-----------------------------------------------------|--------------------------------------|
| Sweetness | Sucrose, glucose, artificial sweetener               | Source of energy                      |
| Saltiness | Sodium, potassium, metal cations                    | Supply of mineral                    |
| Sourness | Acids, which supply proton                          | Activation of metabolism, signal of decay |
| Bitterness | Caffeine, theobromine, quinine, humulone, etc.      | Warning of toxicity                   |
| Umami   | Monosodium glutamate (MSG), disodium inosinate (IMP), disodium guanylate (GMP) | Supply of indispensable amino acids and nucleotides. |
| Astringency | Compounds of tannin series                          | Proteins and bitterness receptors on the mucous surface are to receive |
| Pungency | Capsaicin, allyl isothiocyanate, piperine            | Heat and pain receptors are mediated |

Table 2 Chemical components of each taste sensor.

Table 1 Main materials and features of seven taste qualities.
| Taste sensor               | Lipid                                                                 | Plasticizer                  |
|---------------------------|------------------------------------------------------------------------|------------------------------|
| Saltiness sensor CT0      | Tetradodecylammonium bromide (TDAB), 1-Hexadecanol                      | Diocetyl phenylphosphonate  |
| Soursness sensor CA0      | Phosphoric acid di(2-ethylhexyl) ester (PAEE), Oleic acid, Trioctylmethylammonium chloride (TOMA) | Diocetyl phenylphosphonate  |
| Umami sensor AAE          | Trioctylmethylammonium chloride (TOMA)                                  | Diocetyl phenylphosphonate  |
| Bitterness sensor C00     | Tetradodecylammonium bromide (TDAB)                                     | 2-Nitrophenyl octyl ether (NPOE) |
| (for acidic bitter substances) |                                                                 |                              |
| Bitterness sensor BT0     | Phosphoric acid di-n-decyl ester (PADE)                                 | Bis(1-butylpentyl) adipate (BBPA), Tributyl o-acetylcitrate (TBAC) |
| (for bitter of hydrochloride salts) |                                                                 |                              |
| Bitterness sensor AN0     | Phosphoric acid di-n-decyl ester (PADE)                                 | Diocetyl phenylphosphonate  |
| (for basic bitter substances) |                                                                 |                              |
| Astringency sensor AE1    | Tetradodecylammonium bromide (TDAB)                                     | Diocetyl phenylphosphonate  |
| Sweetness sensor GL1      | Tetradodecylammonium bromide (TDAB), Trimellitic acid                   | Diocetyl phenylphosphonate  |
| Sweetness sensor for negatively charged high-potency sweeteners | Tetradodecylammonium bromide (TDAB)                                     | 2-Nitrophenyl octyl ether (NPOE) |
| Sweetness sensor for positively charged high-potency sweetener      | Phosphoric acid di-n-decyl ester (PADE)                                 | 2-butoxyethyl oleate (BEO)   |