Quantitative Evaluation of the Bitterness of Commercial Medicines Using a Taste Sensor

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The bitterness of 11 commercial medicines was evaluated both by a multichannel taste sensor and in human gustatory sensation tests with 15 volunteers. For basic drugs with amino groups in the molecule, such as quinine, there was a comparatively strong relative response electric potential (mV) of channels 1 or 2, those containing negatively charged membranes and the bitterness determined by human gustatory sensation tests. The suppression of the bitterness of quinine by sucrose and aspartame could be quantified using the artificial taste sensor and the results concurred with those from gustatory sensation tests. The usefulness of the sensor was thus confirmed for this type of compound.

Anionic drugs, such as diclofenac sodium or salicylic acid gave rise in a negative response electric potential in channels 5 or 6, those containing positively charged membranes, seemed to be useful information even though their tastes are being sour rather than bitter.

For drugs with both an amino (cationic) group and carboxylic acid (anionic) group in the molecule, such as theophylline, caffeine, and metronidazole, the relative response electric potential (mV) of channels containing negatively charged membranes was not increased, even though bitterness was observed in human gustatory sensation tests. Therefore, a different design of membrane component is required for more general evaluation of the bitterness of various medicines.

Key words taste sensor; bitterness; human gustatory sensation; quinine; sucrose; aspartame; caffeine

Medicines with a bitter taste are sometimes hard for patients to swallow, and easily give rise to noncompliance and thus decreased therapeutic efficacy. The evaluation of the bitterness of medicines is therefore an important factor in drug design. Taste seems to be have five components, namely, sourness, saltiness, sweeteness, bitterness, and umami.

A multichannel taste sensor, an electric ‘tongue’ with global selectivity, comprises several kinds of lipid/polymer membranes which transform information about substances producing taste into electrical signals. 1–3 These signals are analysed by the computer and the sensor output has been shown to produce different patterns for groups of chemical substances with similar tastes. Using this sensor, the tastes of foodstuffs such as beer, 4 coffee, 5 milk, 6 sake, 7 rice, soybean paste and vegetables can be expressed quantitatively. Even though a taste sensor was just applied to quinine by Takagi et al., 8 there have been no systematic trials using the sensor to evaluate the taste of medicines. In the present study, we evalu-

ated the bitterness of 11 commercial medicines (basic or acidic drugs) using both a multichannel taste sensor and human gustatory sensation tests with 15 volunteers.

The measurement of electric potential was performed using the taste-sensing system SA402 of Anritsu Co., Ltd., Japan (Fig. 1). The electrode set was attached to a mechanically controlled robot arm. The detecting sensor part of the equipment consists of eight electrodes made of lipid/polymer membranes (channels). The lipids used in the present study are listed in Table 1. Each lipid was mixed in a test tube containing poly(vinyl chloride) and diocetylphosphonophosphate as plasticizer, dissolved in tetrahydrofuran in a test tube, and dried on a glass plate at a temperature of 30°C to form a transparent thin film (almost 200 μm thick). Each electrode was made of an Ag wire whose surface was plated with Ag/AgCl, with an internal cavity filled with 3 M KCl solution. The difference between the electric potential of the working electrode and the reference electrode was measured by means of a high input impedance amplifier connected to a computer.

Samples consisting of 1 mM solutions of the following drugs were used in the study: quinine hydrochloride (taken as a standard of bitterness), trimethobutine maleate, dibucaine hydrochloride, metronidazole, betamethasone-21-phosphate, salicylic acid, benzoic acid, diclofenac sodium, theophylline, acetaminophene, and anhydrous caffeine, purchased from Sigma Co. Ltd., U.S.A. Fresh 30 mM KCl solution containing 0.3 mM tartaric acid was used as a reference sample and also to rinse the electrodes after every measurement. The electric potential of the sample was measured as the difference be-

Fig. 1. Taste-Sensing System

Table 1. Lipids Used for the Membranes

<table>
<thead>
<tr>
<th>Channel</th>
<th>Lipid component</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phosphoric acid di-n-decyl ester, diocetyl phenyl-phosphonate</td>
</tr>
<tr>
<td>2</td>
<td>Phosphoric acid di-n-decyl ester, 2-nitrophenyl octyl ether</td>
</tr>
<tr>
<td>3</td>
<td>Hexadecanoic acid, diocetyl phenyl-phosphonate</td>
</tr>
<tr>
<td>4</td>
<td>Diocetyl phenyl-phosphonate</td>
</tr>
<tr>
<td>5, 6</td>
<td>Tetradecylammonium bromide, diocetyl phenyl-phosphonate</td>
</tr>
<tr>
<td>7, 8</td>
<td>Tetradecylammonium bromide, 2-nitrophenyl octyl ether</td>
</tr>
</tbody>
</table>

a) The membrane used for channel 2 was more sensitive than that used for channel 1.

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between the potentials of the sample and 30 mM KCl solution containing 0.3 mM tartaric acid. Each measuring time was set 30 s, and rinsing of electrodes after each measurement was repeated 45 times for about 180 s each time. Samples of each of the 11 drugs (1 mM solutions) were measured three times each according to a rotation procedure.

Figure 2 shows the electric potential response patterns for the 11 drugs. The data from the eight channel inputs has been reduced to a two-dimensional plane. The numbers 1—8 represent the channel numbers, and the scale on the x-axis represents the response electric potential (mV). The sensor output exhibits different patterns for each drug, although some drugs, such as quinine hydrochloride, trimetubine maleate, and dibucaine hydrochloride, show similar profiles. Figure 3 shows the relationship between the relative response electric potential (mV) of channel 1, with a negatively charged membrane, and the bitterness score determined by human gustatory sensation tests as explained in Table 2. In this case, data for channel 1 was adopted as a representative data of channels 1—4 since simultaneous values for relative response electric potential (mV) were obtained in related to channels 2—4.

Although there are some exceptions, basic drugs (represented by closed symbols in Fig. 3) such as quinine, trimethbutin, dibucaine, metronidazole, and betamethasone, tend to be rated as being more bitter and to have a greater relative response electric potential (mV) than acidic drugs (represented by open symbols) such as diclofenac, benzoic acid, salicylic acid, acetaminophen, theophylline, and caffeine. In particular, drugs with quaternary amino groups in the molecule, such as quinine, trimethbutin and dibucaine, showed a comparatively strong electric response in the sensor. The surfaces of the membranes in channels 1—4 were charged negatively, due to dissociation of protons. An electric double layer is formed near the surface of the membrane in aqueous solution; cations such as amino groups accumulate near the surface of the negatively charged membrane. The electric potential then changes gradually from a negative value to zero. Therefore, basic drugs with amino groups are likely to show an increased relative response electric potential (mV).

Quinine was the most bitter drug tested, being scored 10/10 on the gustatory sensation test. The suppression of the bitterness of quinine by sucrose and aspartame could be quantified using the sensor, as shown in Fig. 4. The electric potential changes corresponding to channel 1 correlated well with the gustatory sensation score, thus confirming the usefulness of the sensor. Further, the ability of aspartame to suppress bitterness was found to be 100-fold greater than that of sucrose, as seen not only in the relative response electric potential but also in the gustatory sensation scores. (The effect of aspartame as an artificial sweetening agent has been reported to be 200-fold larger than the effect of sucrose.\(^{23}\))

![Fig. 2. Response Electric Potential Patterns for the 11 Drugs Tested. For explanation, see text.](image)

![Fig. 3. The Correlation between the Relative Response Electric Potential (mV) of Channel 1 for Each of the Sample Drugs and the Bitterness Score Determined in Human Gustatory Sensation Tests](image)

<table>
<thead>
<tr>
<th>Bitterness Score(^{a})</th>
<th>(-10)</th>
<th>(-8)</th>
<th>(-6)</th>
<th>(-4)</th>
<th>(-2)</th>
<th>(0)</th>
<th>(2)</th>
<th>(4)</th>
<th>(6)</th>
<th>(8)</th>
<th>(10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinine concentration (mM)</td>
<td>0.0100</td>
<td>0.0158</td>
<td>0.0251</td>
<td>0.0398</td>
<td>0.0631</td>
<td>0.1000</td>
<td>0.1585</td>
<td>0.2512</td>
<td>0.3981</td>
<td>0.6310</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

\(^{a}\) The value was evaluated by gustatory sensation tests in human volunteers. Before tasting, the volunteer subjects kept the above standard samples in the mouth, and were told the concentration of the standard quinine solution samples and their bitterness score. Then, after tasting 1 ml sample of test drug solution, they were asked to give the sample a bitterness score. All samples were kept in the mouth for 15 s. After tasting the sample, subjects gargled well and waited for at least 20 min before tasting the next sample.
The membranes in channels 5—8 were charged positively. As a typical example, the response electric potential patterns from channel 5 for the 11 drugs was compared with the bitterness score derived from the gustatory sensation test (Fig. 5). Positively charged membranes have been used to evaluate sourness and the correlation between the response electric potentials and bitterness scores from the gustatory sensation tests was not so good. Diclofenac sodium and salicylic acid both showed a large negative response, due to the large negative charge of the drug itself. If sourness had been adopted as a gustatory sensation criteria, a better correlation might have been obtained. Caffeine, theophylline, and acetaminophene contain both anionic and cationic charges in the molecule, even though they are acidic in aqueous solution. Evaluation of this type of drug using the taste sensor seems to require a more sensitive membrane than those used in the present study.

In conclusion, basic drugs with amino groups in the molecule such as quinine, show a comparatively good correlation between the relative response electric potential (mV) of channels 1 or 2 of the taste sensor, which contain negatively charged membranes, and bitterness as determined by human gustatory sensation tests. The suppression of the bitterness of quinine by sucrose and aspartame could also be quantified by this electric sensor. Secondly, for anionic drugs, such as diclofenac sodium or salicylic acid, the positively charged membrane in channel 5 or 6 seemed to be useful even though they are being sour rather than bitter (detail gustatory test in related to sourness was not shown). For drugs with both an amino (cationic) group and a carboxylic acid (anionic) group in the molecule, such as theophylline, caffeine, and metronidazole, the value of the relative response electric potential (mV) of channel 1 or 2 did not increase, even though bitterness was observed in human gustatory sensation tests. Therefore, different types of membrane component will be needed for a complete evaluation of the bitterness of medicines. For example, control of charge density and hydrophobicity of lipid membrane will dissolve the problem.

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References