Regular Article

Taste-Masking Effect of Chlorogenic Acid (CGA) on Bitter Drugs Evaluated by Taste Sensor and Surface Plasmon Resonance on the Basis of CGA–Drug Interactions

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The purpose of this study was to evaluate the taste-masking effects of chlorogenic acid (CGA) on bitter drugs using taste sensor measurements and surface plasmon resonance (SPR) analysis of CGA–drug interactions. Six different bitter drugs were used: amlodipine besylate (AMD), diphenhydramine hydrochloride (DPH), donepezil hydrochloride (DNP), rebamipide (RBM), diclofenac sodium (DCF) and etodolac (ETD). Taste sensor outputs were significantly inhibited by the addition of CGA to all drugs. The inhibition ratio of the taste sensor output decreased in the following order: DPH ≈ DNP > AMD > DCF = RBM = ETD. The association rate constant (k_a) for the interaction between drugs and CGA as evaluated by SPR measurement also decreased in the following order: DPH ≈ DNP > AMD > DCF = RBM = ETD. It was suggested that basic drugs (AMD, DNP, DPH) associate more easily with CGA than acidic drugs (DCF, RBM, ETD). The inhibition ratios (%) of the taste sensor output of bitter drugs caused by CGA and the association rate constants (k_a) between the drugs and CGA were significantly correlated (r = 0.886, p < 0.05, Spearman’s correlation test). Our findings suggest that the taste-masking effects of CGA are due to its direct association with the drugs. CGA may therefore be a useful taste-masking agent for basic drugs.

Key words chlorogenic acid; taste sensor; surface plasmon resonance; interaction; bitterness

The palatability of some commercial medicines has been reported to be comparatively poor, due to the unpleasant bitter taste of the active pharmaceutical ingredient. This may be important, especially for children, as it often causes poor compliance and consequently reduced drug efficacy. Therefore, taste masking may be necessary in order to inhibit the bitterness of some medicines.

Traditionally, the bitter tastes of medicines have been masked by the addition of sweeteners or flavours. At the cognitive level, the perceived inhibition of bitterness occurs in the central nervous system in the brain via taste–taste interactions. A second approach to reducing bitterness is to prevent bitterness perception peripherally, using techniques such as encapsulation, molecular inclusion of cyclodextrins or complexation with ion exchange resin, tannate, fatty acids or food proteins. A third strategy is the application of bitter taste receptor blockers. For example, it has been found that 6-methoxyflavanones can decrease the response of the bitter receptor hTAS2R39 toward diverse bitter compounds. Thus, various methods are available to reduce the bitterness of medicines.

For the application of bitterness-masking agents to pharmaceuticals, there are a couple of basic requirements; the agent should be available in sufficient quantity and known to be safe for consumption. Chlorogenic acid (CGA), an ester of caffeic acid and quinic acid, is one of the most abundant polyphenols in the human diet and possesses anti-inflammatory, antibacterial and antioxidant activities. It is known to be present in fruits, vegetables and coffee (the drink) in high concentrations, and its safety is assured. In our previous study, the addition of a commercial coffee drink to rebamipide solution successfully suppressed the bitterness of rebamipide. Therefore, we expected that CGA would be able to suppress the bitterness of many drugs. However, the bitterness-masking effect of CGA has not yet been evaluated.

The aim of this study was to evaluate taste-masking effect of CGA on bitter drugs using taste sensor measurements and surface plasmon resonance (SPR) analysis of CGA–drug interactions. Six different bitter drugs were used: amlodipine besylate (AMD), diphenhydramine hydrochloride (DPH), donepezil hydrochloride (DNP), rebamipide (RBM), diclofenac sodium (DCF) and etodolac (ETD). These drugs are well-established as bitter medicines and are widely used in clinical practice. The basic drugs AMD, DNP and DPH are used to treat hypertension, Alzheimer’s disease and histamine-mediated allergic conditions, respectively, at doses of 5–10 mg. The acidic drugs RBM, ETD and DCF are used to treat gastric ulcer, inflammation and fever, respectively, at doses of 25–100 mg.

We have previously evaluated the bitterness of various medicines using the Insent taste sensing system (Intelligent Sensor Technology Inc., Atsugi, Japan). We have previously shown that the basic bitter tastes of AMD and DPH could be evaluated using changes in membrane potential caused by adosorption (CPA) values obtained using taste sensor AN0 while the acidic bitterness of RBM could be evaluated using the relative values of taste sensor AE1, both measurements providing good correlation with human sensory tasting. For this reason, in the present study we used CPA values of AN0 sensor output for the basic drugs AMD, DPH and DNP, while

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we used the relative values of the AE1 sensor output for the acidic drugs RBM, DCF and ETB.

Firstly, we measured the bitterness of six drug solutions (AMD, DPH, DNP, RBM, DCF, ETB) mixed with or without CGA using the taste sensor, and calculated the inhibitory ratio of the taste sensor output values with and without CGA, in order to quantify the bitterness inhibitory effect. Secondly, we evaluated the interaction between the drugs and CGA by SPR analysis which is widely used for monitoring the interactions of molecules occurring in very close vicinity to a transducer (gold) surface.\textsuperscript{28–35} The kinetic parameters ($k_a$, $k_d$, $K_D$) were then calculated using TraceDrawer software. Finally, we investigated the correlation between the bitterness inhibitory ratio (%) as evaluated by taste sensor output and the kinetic parameters evaluated by SPR analysis, to clarify the relation of CGA–drug interactions to bitterness suppression by CGA.

**Experimental**

**Materials** Diphenhydramine hydrochloride (Wako Pure Chemical Industries, Ltd., Osaka, Japan), donepezil hydrochloride (Tokyo Chemical Industry Co., Tokyo, Japan), amlo-dipine besylate (LKT Labs, Inc., U.S.A.), etodolac (Wako Pure Chemical Industries, Ltd.), diclofenac (Wako Pure Chemical Industries, Ltd.) and rebamipide (Otsuka Pharmaceutical Co., Tokyo, Japan) were used as models of bitter drugs. Chlorogenic acid (CGA, 3-O-cafeoylquinic acid with a purity $\geq 95\%$) (Cayman Chemical Co., U.S.A.) was used as bitter taste masking agent.

**Methods**

**Taste Sensor Measurement**

The taste sensor SA402B (Intelligent Sensor Technology Inc.) used was the same as that used in our previous studies.\textsuperscript{18,20,22,25–27} The detecting sensor part of the equipment consists of a reference electrode and a taste sensor which acts as the working electrode and is composed of various types of lipid/polymer membrane.\textsuperscript{36} Aqueous solutions (0.01, 0.05, 0.1, 0.5, 1.0, 2.0 mM) of basic drugs (DPH, DNP, AMD) were evaluated using taste sensor AN0, while phosphate-buffered saline (PBS) solutions (0.01, 0.05, 0.1, 0.5, 1.0, 2.0 mM) of acidic drugs (RBM, ETD and DCF) were evaluated using taste sensor AE1.

For the mixed solutions with CGA, we assumed that a dose of 5–10 mg drug would be diluted in 20 mL solvent, the maximum volume of the human mouth. This gives us a calculated concentration for clinical use of 0.5–1.0 mM, and is the basis of the 0.5 mM standard concentration of the basic drugs used in the study. It was decided to test acidic drugs at a higher concentration than basic drugs as, in a previous study, 0.8 mM concentration for clinical use of 0.5–1.0 mM, and is the basis of the 0.5 mM concentration for clinical use of 0.5–1.0 mM, and is the basis of the 0.5 mM standard concentration of the basic drugs used in the study. It was decided to test acidic drugs at a higher concentration than basic drugs as, in a previous study, 0.8 mM concentration for clinical use of 0.5–1.0 mM, and is the basis of the 0.5 mM standard concentration of the basic drugs used in the study. 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Firstly, we measured the bitterness of six drug solutions (AMD, DPH, DNP, RBM, DCF, ETB) mixed with or without CGA using the taste sensor, and calculated the inhibitory ratio of the taste sensor output values with and without CGA, in order to quantify the bitterness inhibitory effect. Secondly, we evaluated the interaction between the drugs and CGA by SPR analysis which is widely used for monitoring the interactions of molecules occurring in very close vicinity to a transducer (gold) surface.\textsuperscript{28–35} The kinetic parameters ($k_a$, $k_d$, $K_D$) were then calculated using TraceDrawer software. Finally, we investigated the correlation between the bitterness inhibitory ratio (%) as evaluated by taste sensor output and the kinetic parameters evaluated by SPR analysis, to clarify the relation of CGA–drug interactions to bitterness suppression by CGA.

**Results and Discussion**

**Taste Sensor Measurements**

The basic drugs AMD, DPH and DNP responded in direct proportion to the logarithm of their concentrations on taste sensor AN0, according to the Weber–Fechner law (Figs. 1(a)). Taste sensor output (AN0) of pure CGA solution at 0.1, 0.5 and 1.0 mM was 0.09 $\pm$ 0.03, 0.45 $\pm$ 0.02 and 0.80 $\pm$ 0.04 mV, respectively. The sensor outputs of basic drugs (0.5 mM) were significantly reduced by the addition of CGA (0.1, 0.5, 1.0 mM) in a dose-dependent manner (Figs. 1(b), (c), (d)). A concentration of 0.5 mM CGA decreased the taste sensor output of 0.5 mM AMD, DPH and DNP by 10.8 $\pm$ 1.5, 46.0 $\pm$ 3.6 and 20.1 $\pm$ 0.9%, respectively.

The acidic drugs RBM, ETD and DCF were used with taste sensor membrane AE1 (Fig. 2(a)). Taste sensor output (AE1) of pure CGA solution at 0.3, 0.8 and 1.4 mM was $-0.84 \pm 0.08$, $-2.62 \pm 0.07$ and $-4.76 \pm 0.05$ mV, respectively. The sensor outputs of the acidic drugs (0.8 mM) were also reduced by ad-
dition of CGA (0.3, 0.8, 1.4 mM) (Figs. 2(b), (c), (d)), although the reduction was less than that for basic drugs. CGA (0.8 mM) decreased the taste sensor output of the acidic drugs RBM, ETD and DCF (0.8 mM) by 10.2 ± 2.0, 9.6 ± 0.6 and 12.2 ± 1.3%, respectively. Overall, bitterness inhibition by CGA decreased in the following order DPH > DNP ≈ AMD ≈ DCF ≈ RBM ≈ ETD when drugs and CGA were mixed at 1 : 1 concentrations.

In the case of taste masking of DNP, Kim et al. reported that bitterness index (BI) of donepezil HCl (orally disintegrating tablet contains 10 mg donepezil HCl) was 5 and that of ion exchange resin drug complex (IRDC) (1 : 1) was 3.08 in human sensation test. The inhibition ratio of the BI was estimated approximately 38%. In the present study, bitter taste sensor output of 0.5 mM DNP was reduced by approximately 20%. From these results, addition of CGA would have effect to inhibit the bitterness of DNP although it seemed to be minimally effective compared to that of IRDC. In the case of taste masking of DPH, Ono et al. reported that bitterness score of 5 mM diphenhydramine hydrochloride (relative score was 1) was reduced by 10 mM β-cyclodextrin (relative score was approximately 0.6). The inhibition ratio was estimated approximately 40%. In our study, bitter taste sensor output of 0.5 mM DPH was reduced by approximately 46% with addition of 0.5 mM CGA. From the result, there would be a possibility that CGA shows valuable taste masking effect for DPH equally to β-cyclodextrin, even though there is difference in concentration of DPH (0.5 mM in our study and 5 mM in the study by Ono et al.).

In our previous study, it was suggested that taste masking effect of 0.05% tannic acid for bitterness of 0.1 mM quinine was 61%. However, application of tannic acid for taste masking agent of bitter drugs has a problem of its own astringency derived from high molecular weight and many phenolic hydroxyl groups. Whereas CGA also belongs to category of polyphenol like tannic acid, its comparatively low molecular weight might be related with the fact that CGA did not show astringency at concentration used in our present study (data not shown). In addition, the concentration of CGA contained in coffee extract was reported approximately 20–60 mg/100 mL, which corresponds to 0.56–1.69 mM. The concentration range of CGA used in this study (0.1–1.4 mM) was almost same or less compared to that contained in coffee. It was suggested the concentrations of CGA added to drug solutions in this study seemed within acceptable range.

Bitter materials are adsorbed on the hydrophobic part of the taste sensor membrane and cause a change in membrane potential by changing the charge density which is reflected by the taste sensor output. Kobayashi et al. also reported that taste sensor outputs are highly correlation with human sensory scores.

The inhibition mechanisms of taste sensor outputs may follow two different patterns. CGA may act on the surface of the
taste sensor membrane, directly competing with the drugs. Alternatively, CGA may act on the drugs themselves (either by directly interacting with them or indirectly, by changing the drugs’ action on the taste sensor) to inhibit their adsorption on the sensor membrane. In the case of basic drugs, the fact that pure CGA solution had no effect on the output of the sensor for basic drugs, AN0, suggests a lower probability of the former pattern than the latter. On the other hand, pure CGA solution (0.01–1.0 mm) had a small effect on the sensor output (0.03–5.0 mV) of AE1 (for acidic drugs). We cannot therefore rule out the possibility that there is some association between CGA and the taste sensor membrane in this case. While we should therefore consider both of the mechanisms described above, we focused on the possibility of an interaction between CGA and drug being responsible for the inhibition of bitterness.

**SPR Measurement** SPR spectra of the pure SPR sensor surface and of the same sensor surface after the deposition of CGA on the sensor are shown in Figs. 3(a) and (b). The clear shift of 0.3° (68.267±0.060 to 68.587±0.053°) of the main SPR peak position (Fig. 3(c)) corresponds to a mass areal density of approximately 300 ng/cm² of CGA deposited on the sensor surface. For self-assembled monolayers formed by alkanethiols on gold, the typical surface density of molecules (when maximum coverage is obtained) is 4.5×10¹⁴ mol/cm². The mass areal density of a typical self-assembled thiol with the same molecular weight as CGA would be approximately 270 ng/cm². This indicates that CGA forms an evenly distributed layer on top of the sensor surface enabling the use of this model surface for studying the interaction strength between different drugs and CGA.

Figure 4 shows the real-time SPR signal response caused by the interaction between CGA and each drug (0.01, 0.05, 0.1, 0.5, 1.0, 2.0 mm). All six drugs responded in a dose-dependent manner. The kinetic fitting by TraceDrawer provided the association rate constant (kₐ), dissociation rate constant (kₖ) and dissociation constant (Kₑ) for the interaction between the drugs and CGA. Acidic drugs (DCF, RBM, ETD) showed lower kₛ values while basic drugs (AMD, DNP, DPH) showed higher kₛ values and lower kₖ values. This suggests that basic drugs associate more easily with CGA than acidic drugs.

The cause of the greater association of DPH or DNP with CGA than AMD is probably differences in structure. The interactions of basic drugs with the CGA surface are probably determined by electrostatic interactions induced by positive charges on the amino groups of the drugs and negative charges on the carboxyl groups of CGA. AMD has a primary amine group, while DPH and DNP have tertiary amines in their structures. The stronger basicity of DPH and DNP with their tertiary amines would allow them to interact more easily with CGA than the weaker basicity of AMD with its primary amine group. The three acidic drugs had low association with CGA, probably due to negative charges on the carboxyl groups in these structures preventing electrostatic interactions with CGA.

**The Relationship between the Bitterness Inhibition Ratios of CGA and Parameters of Drug–CGA Interactions**

Figure 6 shows the relation between the inhibition ratio (%) of taste sensor output and the parameters (Kₑᵢ, kₛ, kₖ) for drug–CGA interaction. Spearman’s correlation coefficient (rₛ) between the bitterness inhibition ratio (%) and parameters Kₑᵢ, kₛ and kₖ were −0.714, 0.886 and −0.486, respectively. The parameter kₛ significantly correlated with the bitterness inhibition ratio (p<0.05). This result indicates that associations between CGA and the various drugs are primarily responsible for suppressing the bitterness of the drugs. The bitterness inhibition ratio showed good correlation with kₛ but not with kᵢ. This indicates that the association between CGA and the various drugs has the greater influence on bitterness inhibition, rather than their dissociation.

Although there was less association between CGA and the acidic drugs, inhibition of bitterness by CGA was also observed with acidic drugs to some extent. One reason for this was thought to be association between CGA and the taste sensor membrane.

Considering the influence of pH on drug solution mixed with CGA for the character or solubility of drug caused by acidity of CGA, ionic mole fraction of 6 drugs (AMD, DNP, DPH, RBM, DCF, ETD) at each pH condition was calculated by Marvin Sketch (ChemAxon). The pH of each drug solution...
with or without CGA were all around 6 and the ionic mole fractions of drugs were predicted 99–100%. From the fact, it was thought that the solubility of the drugs would not be changed by mixing CGA in this study.

When discussing the application of CGA as a bitterness inhibitor, the taste of CGA itself should also be considered. We have already confirmed that 0.1–1.4 mM CGA solutions used in this study show a slight sour taste but did not show bitterness at all in human gustatory sensation test as our pilot study (data not shown). In our previous study, we showed that tartaric acid with strong sourness decreased the bitterness of branched chain amino acids in human sensation tests. However, a slight sour taste and negligible bitter taste of CGA at low concentration used in this study would not have a risk to affect taste of targeted drug.

Further experiments using human gustatory sensation testing would confirm the bitterness inhibitory effect of CGA for bitter drugs. However, human sensation tests are associated with some ethical problems, especially when testing toxic drugs in healthy subjects. In order to reduce these risks, it would be useful to be able to predict the bitterness of pharmaceutical medicines using an artificial taste sensor to reflect human taste. The Insent taste sensing system used in this study has been confirmed as a useful tool for predicting the taste-masking potential of various products and is now widely used to guide the screening of taste-masking agents.

In addition to evaluating the taste-masking effects of CGA on drugs using the taste sensor, we evaluated the interaction between the drugs and CGA using SPR. This method allowed us to examine the mechanism of the bitterness inhibiting effect of CGA. Our findings suggested that an interaction between CGA and the bitter drugs contributed to the bitterness-masking effect of CGA. This method, using a combination of taste sensor and SPR measurements, will be useful for studies of taste masking in which the interaction between bitter drugs and taste-masking agents are examined.

Conclusion
The present study investigated the taste-masking effect of CGA on bitter drugs and the interaction between CGA and these drugs. Bitterness inhibition by CGA as evaluated by taste sensor measurement decreased in the following order DPH > DNP > AMD > DCF > RBM > ETD. The association rate constant ($k_a$) between the drugs and CGA as evaluated by SPR measurement decreased in the following order DPH > DNP > AMD > DCF = ETD = RBM. From the good cor-

![Fig. 4. SPR Signal Response during the Interaction of Drugs (0.01, 0.05, 0.1, 0.5, 1.0, 2.0 mM) with the CGA Deposited on the SPR Sensor Surface (a) AMD, (b) DPH, (c) DNP, (d) RBM, (e) ETD and (f) DCF.](image)

![Fig. 5. Association Rate Constant ($k_a$) and Dissociation Rate Constant ($k_d$) between the Drugs and CGA Analyzed Using TraceDrawer. Black dots indicate basic drugs (AMD, DNP, DPH) and grey dots indicate acidic drugs (RBM, DCF, ETD). ($n=4$, mean±S.D.).](image)
relation between the bitterness inhibition ratio predicted by the taste sensor and the association rate constant ($k_a$) of the drugs and CGA, it was suggested that the taste-masking effect of CGA is due to its association with the drugs. CGA would therefore be useful as a taste-masking agent, especially for basic bitter drugs.

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Conflict of Interest The authors declare no conflict of interest.

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