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Original Article

Enhancement of Combined Umami and Salty Taste by Glutathione in the Human Tongue and Brain

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Abstract

Glutathione, a natural substance, acts on calcium receptors on the tongue and is known to enhance basic taste sensations. However, the effects of glutathione on brain activity associated with taste sensation on the tongue have not been determined under standardized taste delivery conditions. In this study, we investigated the sensory effect of glutathione on taste with no effect of the smell when glutathione added to a combined umami and salty taste stimulus. Twenty-six volunteers (12 women and 14 men; age 19–27 years) performed a sensory evaluation of taste of a solution of monosodium L-glutamate and sodium chloride, with and without glutathione. The addition of glutathione changed taste qualities and significantly increased taste intensity ratings under standardized taste delivery conditions ($P < 0.001$). Functional magnetic resonance imaging showed that glutathione itself elicited significant activation in the left ventral insula. These results are the first to demonstrate the enhancing effect of glutathione as reflected by brain data while tasting an umami and salty mixture.

Key words: glutathione, human taste, insular cortex, monosodium L-glutamate, neuroimaging, umami and salty

Introduction

Efforts have been made to enhance taste by adding substances for improving human health. For example, reducing overall sodium intake in the diet without loss of the palatability of the food is expected to result in great individual and public health benefits. A recent position paper (Jinap and Hajeb 2010) cited several studies in which umami substances added to soup at an optimal level reduced sodium content by 30% to 40% (Yamaguchi and Takahashi 1984). Adding umami substances, such as glutamate, could have additional health benefits. Ingesting glutamate has been shown to reduce weight gain, fat deposits, and plasma leptin concentration in animals (Kondoh and Torii 2008; Kondoh et al. 2009; Nakamura et al. 2013). In humans, glutamate reduces energy intake from sweets and high-fat snacks (Imada et al. 2014).

Furthermore, some substances, such as γ-glutamyl-valinyl-glycine, act on calcium receptors on the tongue and enhance the sensations

of basic tastes such as saltiness and umami (Ohsu et al. 2010; Maruyama et al. 2012). One of these substances is glutathione, which is tasteless and does not contain sodium. Glutathione is an antioxidant that is synthesized in abundance by human cells and assists in redox homeostasis (Forman et al. 2009). Glutathione also functions in many important processes such as protein and DNA synthesis, enzyme activity, and metabolism (Meister and Anderson 1983). In a study of human participants, individual salty and umami tastes and a salty/umami combination were respectively 1.60, 1.72, and 1.74 times more intense with glutathione (Ohsu et al. 2010). In addition, numerous consumer studies have concluded that glutathione (and its derivatives) enhances complex umami and salty tastes in food such as beef stock (Hong et al. 2010; Jung et al. 2010; Kwon et al. 2011). For example, salty and umami tastes were 1.57 and 2.50 times more intense, respectively, when glutathione and monosodium L-glutamate (MSG) were added to beef stock, while liking was 1.60 times stronger (Jung et al. 2010). These studies demonstrate that glutathione has a positive impact on the taste evaluation. However, to the best of our knowledge, objective evidence demonstrating how glutathione changes brain activation was not evaluated in these studies. In addition, past studies have implied that odor from glutathione may affect the sensory characteristics from descriptive analysis of beef soup containing glutathione (Hong et al. 2010; Jung et al. 2010; Kwon et al. 2011). Using an intra-oral device that prevents retronasal smell (Goto et al. 2015), we can investigate the sensory effect of glutathione on taste with no effect of the smell when glutathione added to a combined umami and salty taste stimulus.

The insular region of the human brain is known as the primary taste cortex and processes basic tastes, including umami and saltiness (Kobayakawa et al. 1999, 2008; Small et al. 1999; de Araujo et al. 2003; Spetter et al. 2010; Nakamura et al. 2011, 2012, 2013; Cerf-Ducastel et al. 2012). Specifically, the middle dorsal insula shows altered activity when participants tasted different concentrations of taste solutions; it plays a major role in processing taste intensity (Small et al. 2003; Kobayakawa et al. 2008; Spetter et al. 2010; Yeung et al. 2016). The ventral anterior insula is associated with processing the presence of a taste stimulus, its corresponding pleasantness, and taste quality (Dalenberg et al. 2015; Hoogeveen et al. 2015). As glutathione enhances the intensity and flavor of saltiness and umami tastes on the tongue (Hong et al. 2010; Jung et al. 2010; Ohsu et al. 2010), we hypothesized that the effect of glutathione related to umami/salty stimulus would be reflected in the insula. Thus, the aim of this study was to investigate the taste-enhancing effect of glutathione while tasting an umami and salty mixture both on the tongue and in the brain. We investigated those enhancing effects by using a standardised taste delivery system that delivers taste solutions on the tongue only with no effect of the smell (Goto et al. 2015); we also assessed corresponding changes in brain activation via functional magnetic resonance imaging (fMRI).

Materials and methods

Participants

Twenty-nine volunteers (14 women and 15 men; age range: 19–27 years; mean age ± SD: 21.6 ± 2.2 years; body mass index [BMI] range: 16.7–25.7 kg/m^2; mean BMI ± SD: 20.2 ± 2.14 kg/m^2) were recruited for the study. All participants were nonsmokers, physically healthy, nonobese, right-handed, ate 3 regular meals per day, and did not have tongue deformities. The exclusion criteria included oral complaints, nasal allergies or obstruction within 1 week prior to fMRI, history of neurological illness, current use of medication, and the standard fMRI exclusion criteria. Three participants were unable to sense the umami taste in the stimuli during the training session (described in the Training session) and were thus excluded. Therefore, data from 26 participants (12 women and 14 men; age range: 19–27 years; mean age ± SD: 22.0 ± 2.2 years; BMI range: 16.7–25.7 kg/m^2; mean BMI ± SD: 20.3 ± 2.24 kg/m^2) were analyzed. The participants were instructed to sleep well the night preceding the study and fast for 3 h prior to undergoing the fMRI. We standardized their fasting time because the state of hunger or satiety affects insular activities (van Rijn et al. 2015). The work reported in this article complied with the Declaration of Helsinki for Medical Research involving Human Subjects. The Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster approved this study, and written informed consent was obtained from all participants.

Stimuli

Two taste solutions were prepared using distilled water as the solvent. Both contained 10.68 mM MSG and 171.0 mM sodium chloride (NaCl) at the set concentrations assumed to be present in noodle soup. The second solution also contained 5.26 mM glutathione, which was added as an enhancer. The temperature of the solutions was maintained at 25 °C. Distilled water was used as a baseline and to wash the taste out of participants' mouths between taste stimuli.

Stimulus delivery

Solutions were delivered from a height of 2 m above the ground via an intra-oral device. The custom-made intraoral device was adjusted as required so that participant did not experience gagging, pain, or discomfort (Goto et al. 2015). The device resembled 2 mouth guards bound back-to-back, one covering the upper teeth and the other covering the lower teeth. Solution delivery was controlled by solenoid valves, which were controlled by a computer program. This program also ensured synchrony between the timing of solution delivery and the fMRI scan sequence. The flow rate of the solutions was set at 1.83 mL/s and monitored via flow meters. The suction rate was also strictly monitored and controlled to ensure that there was a constant amount of taste solution or distilled water on the entire tongue throughout the fMRI session. The system was designed to prevent the solution from reaching the soft palate, oral floor, and pharynx. Therefore, no taste remained in the mouth and pharynx during the washing out period of the tongue with water. Tubes were inserted into the front of the device to deliver solutions from the tip to the dorsal, lateral, and posterior parts of the tongue. The solution and airflow for retronasal smell near the throat were removed via a suction tube placed across the posterior part of the tongue; the suction tube was connected to a suction pump (Figure 1). As a result, participants did not need to swallow and experienced no retronasal smell.

Training session

More than 3 days before of the fMRI scanning, all participants attended a training session on an adjustable bed of a computed tomography (CT) scanner. The CT bed allowed us to control the height of the participant's body in the supine position such that it was at the same height as the fMRI scanner. In addition, the CT room in the dental hospital was appropriate for infection control of the saliva from the participants. In the training session, participants were not exposed to any radiation or magnetic field. During the training session, we used the same taste solution delivery system that was used for fMRI. Each participant was delivered the MSG + NaCl

solution for 6 s and distilled water for 15 s alternately for a total of 3 min, with his/her custom-made intraoral device in place. We told to participants that solution with umami taste would be delivered to their whole tongue. Three participants said they perceived salty only and no umami during training session. They did not attend fMRI.

Experimental paradigm and stimuli in fMRI

In each fMRI session, we used both taste solutions (MSG + NaCl and MSG + NaCl + glutathione) as stimuli. Participants were informed that 2 types of solutions would be presented randomly during fMRI scanning but they did not know the contents. Sessions began with 24 s administration of distilled water, followed by 32 pairs of taste stimuli (6 s), and a return to baseline via a distilled-water rinse (15 s). The taste solutions were selected in a pseudorandom order, so that each taste was tested 16 times (Figure 2). Each participant completed 2 successive sessions. Hence, each taste solution was delivered a total of 32 times to each participant. Participants wore an eye mask and received no cues during solution switching. They were instructed to concentrate on tasting the solutions and alert the staff with a squeeze ball if rinsing with distilled water was insufficient or they experienced any other problems. Each session lasted 11 min, and the anatomical scans lasted 9 min. The total scan time per person was 31 min.

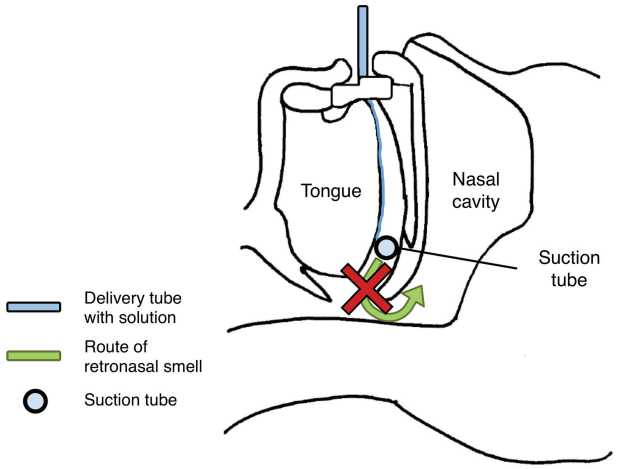

Figure 1. Scheme of the intra-oral device. The intra-oral device was fabricated according to the specification of each individual's anatomy. The intra-oral device delivered the taste solution over the dorsal and lateral surfaces of the tongue. The system was designed to prevent the solution from reaching the palate, oral floor, and pharynx, where the participant would strongly sense the taste stimuli and the taste sensation would remain for a long time. Therefore, no stimuli remained during the washing out period of the tongue with water. Furthermore, a suction tube was placed across the posterior tongue near the throat to suck away solutions and the airflow that might elicit retronasal smells.

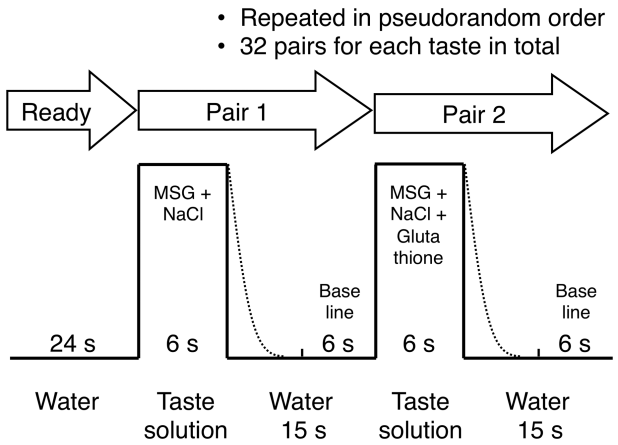

Figure 2. Experimental paradigm. Each session began with 24 s of water administration, followed by administration of 16 tasting and baseline pairs of the taste solution and water. Solutions of MSG + NaCl and MSG + NaCl + glutathione were delivered in a pseudorandom order. There were 2 sessions, and each solution appeared 32 times in total. During fMRI analysis, the first 9 s of each water administration period was modeled as a transition period, during which all residual taste was removed from participants' tongues, and the following 6 s of distilled water administration was set as the baseline.

fMRI data acquisition

Images were acquired using a 3.0-T whole-body MRI scanner in the 3-T MRI Unit housed at The University of Hong Kong. Functional images were obtained using a T2*-weighted gradient-echo echo-planar imaging (EPI) sequence (TR [repetition time] = 3000 ms, TE [echo time] = 30 ms, flip angle = 80°, field of view [FOV] = 220 mm, matrix size = 80×80 pixels, voxel size = 3 mm × 3 mm × 3 mm, slice thickness = 3.0 mm, gap = 0.5 mm). Each EPI volume consisted of 31 axial slices in descending order. For anatomical reference, T1-weighted images were obtained using 3-dimension magnetization-prepared rapid gradient echo sequences (TR = 6.9 ms, TE = 3.1 ms, flip angle = 8°, FOV = 250 mm, voxel size = 1.0 mm × 1.0 mm × 1.0 mm) for each subject.

Sensory evaluation of taste with and without glutathione

Distinguishing of solutions with and without glutathione

Right before commencing fMRI, we presented taste solutions of MSG + NaCl and MSG + NaCl + glutathione to the participants. They were the same solutions as used for fMRI, but were in the cups. Each solution was tasted as one mouthful of approximately 11 mL (1.83 mL/s × 6 s, which was the volume of taste solution to be delivered each time during fMRI). The cups were labelled as solutions 1 and 2, and their contents were not disclosed to the participants. Participants were instructed to taste the solutions one by one without swallowing, spit each one out, and rinse with ample distilled water in between. All participants reported that solutions 1 and 2 were not the same, and perceived higher intensity of solution 2 (with glutathione). Then, we explained to participants "these 2 types of solutions would be delivered to your tongue randomly with intra-oral device during fMRI scanning. Please concentrate to taste them, and evaluate taste quality and intensity of solution 1 and 2 during fMRI".

Sensory evaluation of taste with and without glutathione during fMRI

Immediately after the fMRI session, participants reported the taste during fMRI data acquisition in the assessment sheet for solution 1 and 2 by addressing the following queries.

Evaluation of taste quality

Descriptive evaluation: please choose appropriate descriptions for taste from the options as "meaty," "brothy," or "long-lasting," and also describe the taste in your own words.

Evaluation of taste intensity

Intensity ratings attributed to glutathione: please rate taste intensity on the Visual Analogue Scale ranging from 0 (tasteless) to 10

(maximum intensity imaginable) for each solution. Data were analyzed using SPSS 20.0 (IBM). Shapiro–Wilk tests were performed to check the normality of the data distribution. The ratings followed a normal distribution; therefore, we performed paired *t*-tests. Statistical significance was set at a level of $P < 0.05$.

fMRI data analysis

Image pre-processing and data analysis were performed using the Statistical Parametric Mapping 8 (SPM8) software package (Wellcome Trust Centre for Neuroimaging) implemented in MATLAB R2012a (The MathWorks, Inc.). For each session, the first 4 volumes of functional images were discarded owing to unsteady magnetization, and the remaining 226 volumes were used in the analysis.

Spatial pre-processing steps were applied to the data prior to statistical analysis. The functional images from each session were realigned to the first image of their respective sessions, and the images from both sessions were realigned together to the mean image (using default settings, "realign: estimate and re-slice"). They were subsequently co-registered with the anatomical image. Both functional and anatomical images were then normalized to the Montréal Neurological Institute template (with voxel sizes of 3 mm × 3 mm × 3 mm and 1 mm × 1 mm × 1 mm, respectively), to allow comparison of voxels from each participant. Functional images were then smoothed with a 10-mm full-width at half-maximum isotropic Gaussian kernel.

Individual level analysis

For individual level analysis, a general linear model was applied to the data. Two regressors (MSG + NaCl and MSG + NaCl + glutathione) were modeled. These regressors were convolved with a canonical hemodynamic response kernel. The tasting periods were designated as 6-s boxcar functions. The final 6 s of every 15 s of distilled water period was set as the baseline (Figure 2). The time series data for each voxel were high-pass filtered with a cut-off period of 128 s to remove low-frequency signal drift. A first-order autoregressive model (AR(1)) was used to remove serial correlations in the data. Data analysis was performed by measuring the taste—baseline difference as a defined linear contrast (Worsley 2001). We used the 6 s baseline because we had confirmed that there was no residual taste in the last 9–10 s of the rinsing period in pilot studies. For each contrast, a collection of *t*-statistic values from every voxel produced a statistical parametric map, which was transformed into the unit normal distribution (SPM *z*). We examined the statistical parametric maps generated by each solution at an initial threshold of uncorrected $P < 0.005$ and cluster size of >10 voxels. Clusters that had a cluster $P < 0.05$ corrected for family-wise error (FWE) were defined as significant. The effect of glutathione was analyzed by determining MSG + NaCl + glutathione minus MSG + NaCl. At this time, a voxel *P* value of <0.01 was applied.

Group analysis

Group effects were assessed using random-effects analysis to allow for population inferences. A paired *t*-test with MSG + NaCl + glutathione and MSG + NaCl was then performed to test the effect of glutathione. We examined the whole brain for significant activation, with the statistical threshold set at an uncorrected peak *P* value of <0.005 and a cluster size of >10 voxels, which produces a desirable balance between Type I and II error rates (Lieberman and Cunningham 2009). We also determined the effect of each solution by separate one-sample *t*-tests. We examined the statistical parametric maps generated by each solution at an initial threshold of uncorrected $P < 0.005$ and cluster size of >10 voxels. Clusters that had a cluster $P < 0.05$ corrected for FWE were defined as significant.

Results

Sensory evaluation of taste with and without glutathione

Evaluation of taste quality

The results of the taste evaluations of the 2 solutions during fMRI but reported immediately after fMRI data acquisition for all participants are shown in Table 1. The number of responses for "meaty" and "long-lasting" from options increased after adding glutathione. Nine participants wrote "salty" as a free word for solution 1 and this number decreased after adding glutathione.

Evaluation of taste intensity

The mean ± SD for the taste intensity ratings were 4.89 ± 1.91 for MSG + NaCl and 6.73 ± 1.96 for MSG + NaCl + glutathione. The increase in taste intensity observed after the addition of glutathione was statistically significant ($P < 0.001$).

fMRI results

Individual level analysis

The activations in the insula elicited by tasting each solution are reported in Table 2 for all participants, and a representative result is shown in Figure 3. That participant showed the activations in the left ventral insula, anterior and mid dorsal insula, striatum, and anterior cingulate cortex. In this individual, the cluster size of the ventral insula was quite small, but we confirmed this was not an artefact.

Group analysis

The activation maps for each solution are described in Table 3 and Figure 4. Significant activation attributable to glutathione alone (i.e., the difference in activations attributed to MSG + NaCl + glutathione minus MSG + NaCl) was observed in the left ventral insula and adjacent to the posterior end of the activation attributed to MSG + NaCl + glutathione (peak voxel at $x = -36$, $y = 8$, $z = -17$; *z*-value = 3.40; $P = 0.001$; cluster size = 17 voxels).

Discussion

Sensory evaluation of taste with and without glutathione

Evaluation of taste quality

Differences in taste type and quality were observed when glutathione was added to the taste solution (i.e., solution 1 vs. solution 2). We added glutathione to the same concentrations of MSG + NaCl but it was interesting that the number of participants who responded

Table 1. Sensory evaluation (evaluation of taste quality) of taste with or without glutathione under standardized taste delivery conditions

	MSG + NaCl	MSG + NaCl + glutathione
Meaty	3	10
Long-lasting	1	9
Brothy	8	6
Salty	9	6

Number of participants reporting the above feelings for each solution.

Table 2. Individual level analysis: activations in the insula for each participant in response to the 2 solutions and the effect of glutathione

Participant	MSG + NaCl		MSG + NaCl + glutathione		Effect of glutathione	
	Left insula	Right insula	Left insula	Right insula	Left insula	Right insula
1					●	●
2	●		●	●	●	●
3	●	●	●	●	●	
4	●		●		●	
5		●	●	●	●	●
6	●	●	●	●	●	●
7	●	●	●	●	●	●
8	●	●	●	●		
9	●	●	●	●	●	●
10						
11	●	●	●	●	●	
12	●	●	●	●	●	●
13		●	●	●	●	●
14	●	●	●	●	●	
15	●	●	●	●		●
16	●	●	●	●		
17		●	●	●	●	●
18		●	●	●	●	
19	●	●	●	●	●	●
20	●	●	●	●	●	
21						
22	●	●	●	●		
23						
24	●	●	●	●		
25	●		●	●	●	●
26			●		●	

The black circles represented activations identified in individual analysis. Effect of glutathione, the activations attributed to MSG + NaCl + glutathione minus MSG + NaCl.

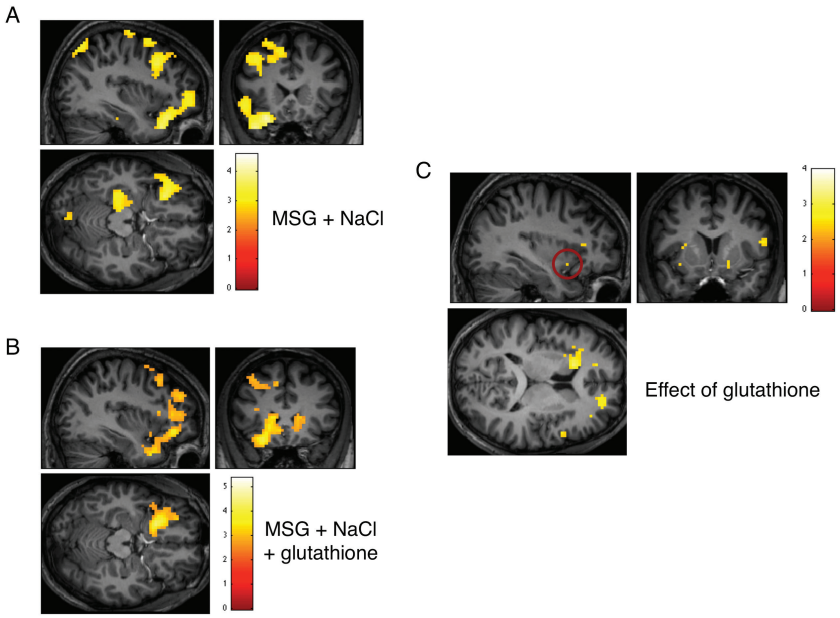

Figure 3. Effect of adding glutathione on brain activations in individual level analysis. (**A**) The activation map of MSG + NaCl. (**B**) The activation map of MSG + NaCl + glutathione. (**C**) Differences in activations attributed to MSG + NaCl + glutathione minus MSG + NaCl were observed at the left ventral insula (peak voxel: –36, 8, –14; $z = 1.92$, cluster size = 1 voxel), anterior and mid dorsal insula, striatum, and anterior cingulate cortex.

that the taste was meaty and long-lasting increased, while those who responded that it was salty and brothy somewhat decreased after adding glutathione. The definitions of the terms used in this study were as follows. "Umami" was "elicited by the most common amino acid, L-glutamate, a cleavage product of all proteins" (Lindemann et al. 2002). The "meaty" was "tasting a lot of meat," "long-lasting"

Table 3. Brain regions activated by the 2 solutions and the effect of glutathione in the group analysis

Region	MNI coordinates[a]			*z* Value	Voxel *P*[b]	Cluster size (voxels)[b]	Cluster P_{FWE}
	x	y	z				
Individual solutions							
MSG + NaCl							
Insula/	−51	23	4	3.94	0.000	667	0.003
Orbitofrontal cortex/	*−30*	*23*	*−14*	3.81	0.000		
Inferior frontal gyrus L	*−45*	*32*	*1*	3.71	0.000		
Brainstem L	−6	−4	−11	3.82	0.000	77	0.632
Caudate R	27	−7	16	3.78	0.000	26	0.918
	21	*−1*	*16*	3.63	0.000		
Precentral gyrus R	57	5	22	3.05	0.001	37	0.863
MSG + NaCl + glutathione							
Insula/	−30	23	−14	4.13	0.000	598	0.009
Orbitofrontal cortex/	*−33*	*44*	*−8*	3.94	0.000		
Inferior frontal gyrus L	*−48*	*38*	*4*	3.26	0.001		
Caudate L	−12	8	19	3.26	0.001	248	0.142
Putamen R	30	−16	1	3.24	0.001	24	0.918
Cerebellum R	12	−40	−20	2.83	0.002	11	0.966
Cerebellum L	−12	20	7	2.73	0.003	10	0.969
Effect of glutathione[c]							
Insula L	−36	8	−17	3.40	0.001	17	0.961

L, left; R, right; FWE, corrected for familywise error.

[a]Italics indicate that a peak falls under the same cluster as the preceding peak.

[b]The cluster size and voxel *P* were taken at the statistical threshold of voxel $P < 0.005$ (uncorrected) and cluster size > 10.

[c]Effect of glutathione was assessed by paired *t*-test between activations from MSG + NaCl and MSG + NaCl + glutathione.

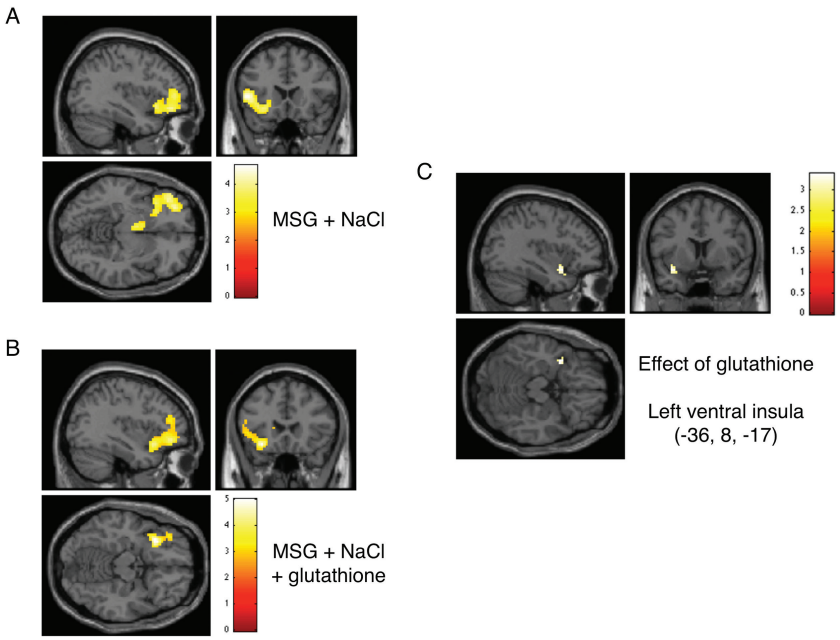

Figure 4. Effect of adding glutathione on brain activations in the group analysis. (**A**) The activation map of MSG + NaCl. (**B**) The activation map of MSG + NaCl + glutathione. (**C**) The difference in activation attributed to MSG + NaCl + glutathione minus MSG + NaCl was observed at the left ventral insula (peak voxel: −36, 8, −17; $z = 3.40$, cluster size = 17 voxels).

was "continuing for a long period of time" and "brothy" was "a thin soup" (Cambridge Dictionary) (all participants received a British-style education). Therefore, it was suggested that the enhancement was not equal for both MSG and NaCl. In this study, participants only evaluated the taste quality for a mixture of MSG and NaCl, not the individual qualities of these. Quantitative evaluations, such as separate Visual Analogue Scale scores of taste change on MSG and NaCl were not performed. In addition, studies should be performed in the future to determine the psychophysical effects of glutathione in more detail.

The increase in the number of participants who responded that taste was "long-lasting" indicated changes in the temporal sensory properties of taste sensation in response to the addition of glutathione. This may be owing to the participants perceiving higher taste intensity to the solution with glutathione. Further, it took longer time to wash out the solution with glutathione. In the future,

time-intensity recordings of taste stimuli on tongue (Goto et al. 2015) would be useful for a better understanding of the temporal sensory property of taste with glutathione. For fMRI analysis, we carefully designed the experimental paradigm to avoid the effect on brain activities caused by persistence of tastes during washing out. Specifically, only last 6 s of distilled water administration was set as the baseline (Figure 2).

The change in taste quality after adding glutathione did not involve the effect of smell as none of the participants perceived any smell during the fMRI sessions. Furthermore, taste stimuli were delivered only on the tongue with our system, but not on the soft palate, oral floor, pharynx, or gut. Therefore, we assume that the effect of glutathione was only on the tongue.

Basic physiological research on the effects of glutathione on taste receptor cells would help explain the changes in the quality of MSG and/or NaCl taste, however, we could not find such a report in the literature.

Evaluation of taste intensity

In our study, the taste of the MSG + NaCl solution was 1.38 times more intense with glutathione. This is in agreement with the findings of Ohsu et al. (2010) who report an enhancing effect of glutathione on combined umami and salty tastes. We assume that such taste intensity enhancements could be explained by the presence of calcium-sensing receptors, which are similar to taste receptors, on the tongue (Ohsu et al. 2010). Glutathione is sensed via calcium-sensing receptors, and some of other calcium-sensing receptor agonists such as γ-glutamyl-valinyl-glycine have been found to enhance taste in a similar fashion, while their effects were suppressed by a receptor inhibitor (Ohsu et al. 2010; Maruyama et al. 2012).

fMRI data

To our knowledge, this is the first study to provide neuroimaging data demonstrating the taste enhancement effect of glutathione. In the brain, the significant activation attributed to glutathione alone (the difference in activations attributed to MSG + NaCl + glutathione minus MSG + NaCl) was observed in the left ventral insula. The activations in the dorsal insula were not significant on group analysis, while they were observed in the first level (individual) analysis.

Recent studies investigating brain activation in humans has found that the left ventral anterior insula is associated with processing the presence of a taste stimulus as well as its corresponding pleasantness (Dalenberg et al. 2015), and the right ventral insular cortex is associated with evaluating taste quality effects (Hoogeveen et al. 2015). On the other hand, the dorsal insular cortex is associated with taste concentration or intensity effects (Small et al. 2003; Grabenhorst et al. 2008; Kobayakawa et al. 2008; Spetter et al. 2010; Veldhuizen et al. 2010; Dalenberg et al. 2015; Hoogeveen et al. 2015; Yeung et al. 2016), whereas the ventral anterior insular cortex is not (Hoogeveen et al. 2015). All but one of those studies focused on sweet, salty, sour, or bitter tastes, but not on umami taste. A study by Grabenhorst et al. (2008) assessed umami taste, but the solution used (MSG + IMP) was different from that used in our study. Therefore, it is difficult to directly compare the results of these studies to our results, but the activation in the left ventral anterior insula may predominantly reflect the taste quality effect rather than the intensity effect.

Study limitations and future prospects

This study used fMRI to characterize neural activity patterns in humans that may underlie the effects of glutathione on the quality and taste of MSG and NaCl at concentrations resembling those typically found in noodle soup. As for the evaluation of changes in taste in response to glutathione, future studies should include quantitative evaluations to know the balance of taste change on MSG and NaCl, respectively, and time-intensity recording to analyze temporal sensory property of glutathione. As for fMRI, we could not perform several sets of experiments owing to limitations of the fMRI scan time and participant fatigue. Therefore, we did not investigate the effect of glutathione on pure MSG or NaCl, and instead chose a combined umami and salty stimulus, which mimicked actual noodle soup consumed in daily life. In the future, various concentrations, temperatures, and combinations of tastes should be tested to determine the optimal concentration of glutathione as a diet ingredient. It should be tested how much NaCl levels can be reduced by the addition of glutathione without negatively affecting taste. In addition, we should test how glutathione changes ratings of liking considering that food consumption pleasantness is an important aspect of the chemical senses.

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Conflict of interest

Mitsubishi Shoji Foodtech Co., Ltd. partly supported the study financially; they did not have any influence over the study conception, design or interpretation, or the decision to publish the data. Yuki Ito is employed by Mitsubishi Shoji Foodtech Co., Ltd. The authors have no patent or stock ownership nor do they have any membership of a company board of directors, membership of an advisory board or committee for a company, or consultancy for or receipt of speaker´s fees from a company which would affect this research or publication. All materials used in this study were commercially available.

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