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Cortical representation of taste-modifying action of miracle fruit in humans

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Red berries of a tropical plant called miracle fruit, *Richadella dulcifica*, reduce the sour and aversive taste of acids and add sweet and palatable taste. To elucidate the brain mechanism of this unique action of miracle fruit, we recorded taste-elicited magnetic fields of the human cerebral cortex. The initial taste responses were localized in the fronto-parietal opercular/insular cortex reported as the primary taste area. The mean latency of the response to citric acid after chewing miracle fruit was essentially the same as that for sucrose and was 250–300 ms longer than that for citric acid. Since it is known that stimulation with acids after the action of miracle fruit induces both sweetness and sourness responses in the primate taste nerves, the present results suggest that the sourness component of citric acid is greatly diminished at the level of subcortical relays, and mostly sweetness information reaches the cortical primary taste area. We propose the idea that the qualitative aspect of taste is processed in the primary taste area and the affective aspect is represented by the pattern of activation among the different cortical areas.

Introduction

Miracle fruit, red berries of a native shrub, *Richadella dulcifica*, in tropical West Africa, contains a taste-modifying protein, miraculin (Theerasilp and Kurihara, 1988), which has the unusual property of reducing sour taste of acids and adding sweet taste (Kurihara and Beidler, 1969), e.g., the taste of lemon changes into that of orange. One explanation for the taste modifications by miracle fruit is that this dramatic effect comes from the addition of sweetness to sourness, resulting in the suppression of sourness in the central nervous system rather than direct suppression of sourness at the receptor level (Kurihara and Beidler, 1969; Bartoshuk et al., 1974). The sweetness could be induced by the interaction of the sugar component of this glycoprotein to sweet receptors on taste cells as a result of conformational changes of the cell membrane by acid stimulation (Kurihara and Beidler, 1969). As supportive evidence of this notion, Brouwer et al. (1983) showed that the taste nerves of the monkey actually conveyed both acid and sugar information in response to acids after treatment of the tongue with miraculin. Hellekant et al. (1998) also showed by single fiber analyses of the chorda tympani nerve in chimpanzees that a subset of fibers responsive exclusively to sweeteners but not to acids responded to acids as well as to sweeteners after miraculin.

It may be too early, however, to explain the action of miracle fruit only by mixture effects because the additional treatment of the tongue with gymnemic acid, an anti-sweet substance, after miracle fruit suppressed the sweetness completely but recovered the sourness to about 80% of the original sourness of citric acid (Bartoshuk et al., 1974), suggesting that about 20% sourness was suppressed at the receptor level. Recent progress of molecular mechanisms of taste receptors including sour receptors would reveal the action of miraculin possibly occurring at the taste cell level.

The brain mechanisms of this taste-modifying action are still unknown. Why do we taste the dominant sweetness and perceive palatability if both sourness and sweetness information is conveyed through the taste nerves to the brain? Where in the brain is the sourness information suppressed, in the cortex or at the subcortical levels? To address these questions and to elucidate the cortical processing of taste information, we recorded taste-elicited magnetic fields of the human cerebral cortex and compared them before and after taste-modifying action of miracle fruit. Magne-

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toencephalography (MEG) is one of the non-invasive functional brain imaging techniques. MEG has good temporal resolution in comparison to functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) and can give a good estimation of the localization of the activity much more precisely than electroencephalography (Murayama et al., 1996; Kobayakawa et al., 1996a,b; Yamamoto et al., 2003).

Methods

A total of 28 subjects participated in the pilot study and received screening tests where they were examined for several aspects concerning suitability as subjects including adequate patience in the shielded room, good compatibility of the tongue with the flow chamber, good evoked MEG responses and long-lasting and remarkable taste-modifying action of miracle fruit. They were neurologically healthy volunteers aged from 22 to 35 years: 10 males and 18 females. 7 males and 12 females were right-handed, and 3 males and 6 females were left-handed. Handedness was assessed with the Edinburgh scale (Oldfield, 1971). They were informed about the nature of the experiment and agreed to be subjects. The experiment was conducted in accordance with the revised version of the Helsinki declaration and was approved by the Osaka University Ethical Committee.

The taste stimuli used were 0.05 M citric acid and 0.5 M sucrose. At these concentrations, all the subjects reported that the citric acid was sour and unpleasant and that the sucrose was sweet and pleasant. These solutions were made just before the experiment by dissolving the reagent grade chemicals into distilled water. The solutions and water were used at room temperature (24±1 °C). To analyze the taste-modifying action, responses to citric acid were recorded after chewing one or two pieces of miracle fruit berries for 3 min. Miracle fruit was grown by Dr. Yoshie Kurihara, and the berries were stored at −80 °C until the subjects chewed in the experiments.

Each subject was comfortably seated on a non-magnetic chair in a magnetically shielded room. A newly manufactured computer-controlled stimulus delivery system, essentially the same as that employed by Kobayakawa et al. (1996b, 1999), was constructed to apply taste solution and water rinses through a Teflon tube. Our stimulus presentation method fulfilled the standards (except for temperature control at 36 °C) advocated by Evans et al. (1993) to evaluate the precise chemosensory event-related potentials. Although Kobayakawa et al. used a small hole in the Teflon tube to deliver the stimulus to the tongue, we used a flow chamber (1 cm diameter and 0.8 cm length) covering the anterior part of the subject's tongue.

In order to verify that the exposed tongue in the chamber is so rapidly stimulated as to satisfy the criterion (less than 50 ms rise-times to reach 70% of maximum strength) by Evans et al. (1993), we measured the time difference between two electrodes put at the inlet and at the outlet of the flow chamber with a model tongue made of silicon rubber, the conductivity measurement and the same delivery manner as described above. The conductivity measurement was followed by Kelling and Halpern (1986) with a small modification, briefly, the potential difference between the two electrodes was measured with a differential amplifier in parallel with the conductivity cell where a 1 V, 10 kHz sine wave was led. With this method, as Kelling and Halpern showed, electric conductivity was not linearly corresponding to tastant concentration. The time differences between the onset of the stimulus at the inlet and 70% of the maximal signal amplitude at the outlet were 23.8±1.6 ms (mean±SD, $n=10$) and 25.0±1.3 ms (mean±SD, $n=10$) for 0.05 M citric acid and a mixture of 0.5 M sucrose and 0.1 M NaCl (0.1 M NaCl was added to the sucrose solution during measurement), respectively.

A small air bubble was inserted between the rinse and taste solution to prevent diffusion of fluids. The flow rate of the water and stimuli was 100 ml/min. The duration of the rinse was 40 s. The duration of each taste solution was 0.4 s. This short duration is enough to elicit taste sensation for more than 1 s (Halpern, 1991) and to make quality evaluation (Kelling and Halpern, 1986). The outlet from the chamber was led to outside of the shielded room, and the taste solutions and water rinses were discarded. Taste solutions were colored red to allow their detection by an optical sensor, but water was not colored. The sensor was positioned immediately before the entry to the flow chamber. This onset of taste stimulation provided a trigger signal for MEG averaging. The subjects were instructed not to change their head positions, to keep their eyes open and watch a fixed point in front of them.

The subjects participated in the following series of sessions with intermissions: each session contained (1) 0.05 M citric acid, (2) 0.5 M sucrose, (3) 0.05 M citric acid after chewing 1 or 2 pieces of miracle fruit berries or (4) water as the control. Through these examinations, we selected 7 subjects. The order of stimulus delivery was random for citric acid, sucrose and water, and the last trial was citric acid after miraculin. Each stimulus was applied 40 times. The intermission was between 30 and 60 min. Soon after each session, the subjects were asked to describe each stimulus, and we confirmed that they described citric acid as sour, sucrose as sweet, citric acid after miracle fruit as mostly sweet with slight sourness toward the end of the session, and water as tasteless.

Brain magnetic fields were recorded with a whole-cortex, 122-channel SQUID system (Neuromag-122™, Neuromag Ltd. Finland). MEG signals were recorded through a 0.03–100 Hz analog bandpass filter and an A/D converter which sampled data at 400 Hz. Stimulus-related epochs with duration of 1000 ms, including a 200 ms pre-stimulus baseline, were averaged more than 40 times. Epochs containing eye blink artifacts were rejected from the averaging process. Averaged data were digitally filtered with a bandpass of 0.1–30 Hz. Source estimation was carried out by the equivalent current dipole (ECD) method between the latencies of 0 and 1000 ms. In the single ECD analysis, all the MEG sensors were divided into 34 overlapping local sensor groups having 14–20 sensors each (Imada et al., 1996; Nakagawa et al., 2004). Among the calculated ECDs, those that satisfied the following criteria were selected: goodness-of-fit >80%, a 95%-confidence volume <2000 mm^3, and continuously active for more than 10 ms.

The exact location of the head with respect to the sensors was found by measuring the magnetic signals produced by three indicator coils placed at known locations on the scalp. The location of each coil with respect to three landmarks, the nasion and two preauricular points, was determined with a 3D digitizer (3space Isotrak II, Polhemus Inc., USA). For estimating source location, 3D MRI scans were obtained for all subjects (AIRIS-II, Hitachi, Japan; 0.3 T).

The mean values and standard errors of the means (means± SEMs) were calculated for the latency. Data were analyzed by one-way ANOVA, with the level of significance set at $p<0.05$. When a significant main effect of treatment was revealed, *post hoc* multiple comparisons of means were performed using Tukey's HSD test.

Results

Reliable and reproducible data were obtained in 7 subjects. They were 5 males and 2 females; 3 males and 1 female were right-handed, and 2 males and 1 female were left-handed.

The representative MEG responses among the 122 recording points to each of the 3 taste stimuli, i.e., citric acid, sucrose, and citric acid after miracle fruit, are shown in Fig. 1. The response to sucrose was sluggish with longer onset time in comparison with that to citric acid, and the response to citric acid after miracle fruit was similar to that to sucrose. Water application did not induce any noticeable response. When the first ECD after onset of stimulation was estimated in the cerebral cortex using a one-dipole model and was superimposed on the subject's MRI, the source of the activity was detected in the middle insula and adjoining parietal operculum that is suggested to be the "primary taste area" (PTA) by Kobayakawa et al. (1999) and Ogawa et al. (2005).

For the assessment of validity of the response patterns shown in Fig. 1, averaged responses in the same subject to citric acid, sucrose, citric acid after miracle fruit and water from all the 24 recording points were superimposed on the same graphs (Fig. 2).

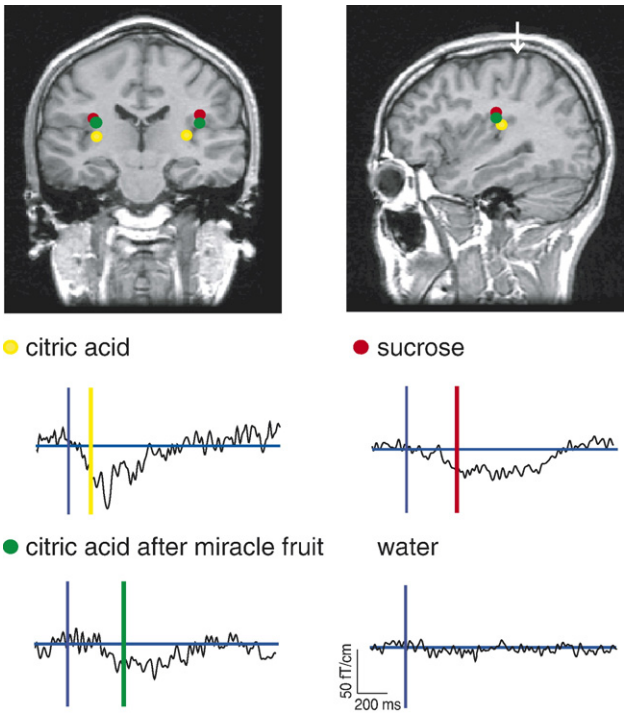

Fig. 1. Cortical area activated and averaged MEG responses evoked by 0.05 M citric acid, 0.5 M sucrose, 0.05 M citric acid after chewing of miracle fruit and distilled water (from one of the subjects). The representative responses were obtained from one recording point immediately dorsal to the left ear. Note that application of distilled water induced little response. Yellow, red and green circles on the MRI indicate the equivalent current dipole positions in the parietal opercular insular cortex for citric acid, sucrose, and citric acid after miracle fruit, respectively. The right side of the MRI corresponds to the right side of the brain. Vertical blue line, onset of stimulation; vertical yellow, red and green lines, latencies of the first appearance of the dipole for citric acid, sucrose and citric acid after miracle fruit, respectively. The first detection of the ECD in the PTA was 113, 284 and 318 ms for citric acid, sucrose, and citric acid after miracle fruit, respectively. White arrow in the left sagittal section shows the central sulcus.

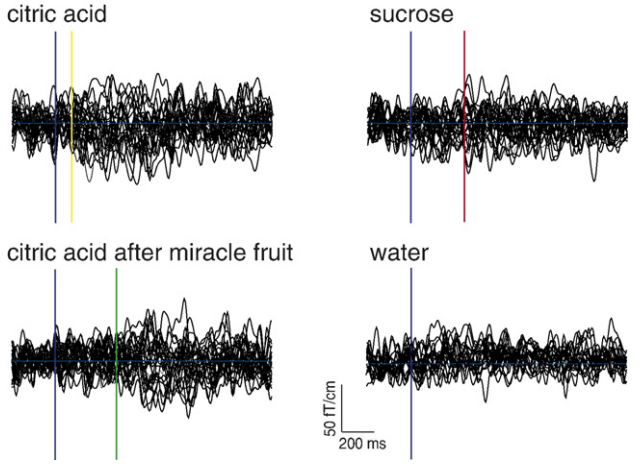

Fig. 2. The magnetic responses to citric acid, sucrose, citric acid after miracle fruit and water obtained from the same subject as in Fig. 1. Averaged responses for each of the stimuli from 24 recording points were superimposed, aligned to the stimulus onset. Vertical blue, yellow, red and green lines denote the same as shown in Fig. 1.

As shown in this figure, sucrose, and citric acid after miracle fruit induced responses with longer latencies than that of citric acid. Water evoked essentially no response. To further assess the validity of the above findings across subjects, representative averaged responses obtained from a prescribed electrode in each subject were examined by exhibiting superimposed traces (Fig. 3). The time courses and the magnitudes of responses were very similar among the 7 subjects for each of the 3 stimulations. As shown in Fig. 3, it is apparent that patterns of responses to citric acid after miracle fruit are similar to those to sucrose compared to those to citric acid. The most convenient quantitative measure to distinguish the responses was to measure latencies, or the time at which the first detection of the ECD was detected after the onset of taste stimulation. The mean±SEM values obtained from all the 7 subjects were 112±4, 396±66 and 373±95 ms for citric acid, sucrose, and citric acid after miracle fruit, respectively. According to one-way ANOVA, the main effect of sample was significant ($F(2,12)=5.810$: $p<0.05$). Further statistical analysis (Tukey's HSD test) showed that the latency for citric acid was significantly shorter than that for sucrose and for citric acid after miracle fruit ($p<0.05$).

In the present study, the PTA where the first taste-elicited ECDs were most frequently detected across subjects was located in the insula/operculum near the transitional zone of the frontal and parietal lobes. We identified the central sulcus which is the boundary between the frontal and parietal lobes and categorized the source of activity as either anterior or posterior to the central sulcus. The results show that the first ECD was obtained in the frontal lobe in 4 subjects and in the parietal lobe in 3 subjects. It is noted here that 'frontal lobe' referred to by Small et al. (1997b) is more anterior than our 'frontal lobe'. Although there seemed to be a tendency for activation to sucrose and citric acid after miracle fruit to be located more anteriorly and for activation to citric acid to be found posteriorly (as suggested in Fig. 1), further analysis is needed to provide clear evidence for chemotopy in the PTA.

Besides the PTA, other areas of the cortex were also activated by taste stimuli, i.e., ECDs were estimated outside the taste areas. These areas included the superior temporal sulcus, central sulcus,

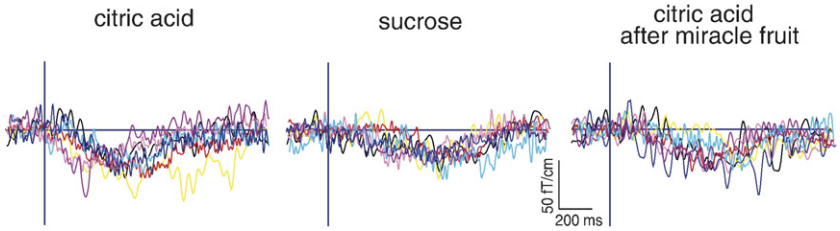

Fig. 3. The representative averaged MEG responses to citric acid, sucrose, and citric acid after miracle fruit in 7 subjects. Responses were displayed in different colors for each subject. Responses for each the stimuli from a prescribed recording point dorsal to the left ear were superimposed, aligned to the stimulus onset. Responses obtained from each subject were displayed with different colors. Vertical blue line denotes the onset of simulation.

lingual gyrus, middle temporal sulcus, cuneus, angular gyrus, parahippocampal gyrus and supramarginal gyrus. The cortical areas activated differed depending on the kind of taste stimuli and among the subjects. However, no apparent difference was detected between the left and right hemispheres for these activated areas. Fig. 4 shows a proportional representation of the areas that exhibited ECDs during the first 1 s after onset of stimulation in the 7 subjects, i.e., the larger proportion indicates that cumulative numbers of ECDs are larger in the region. As shown in this figure, the pattern of activation across the areas was very similar between citric acid after miracle fruit and sucrose, but was different from the pattern for citric acid.

Discussion

Studies in non-human primates have suggested the existence of two taste areas (PTA and STA) in the cerebral cortex: the PTA is in the transitional zone of the frontal operculum and the anterior insular cortex and the STA is in the caudolateral OFC (Rolls et al., 1990; Ogawa, 1994; Rolls, 1997), and Ogawa (1994) includes the somatosensory area 3 in the PTA and precentral opercular area and areas 1–2 in the STA. Non-invasive recordings from human brain (Kinomura et al., 1994; Murayama et al., 1996; Kobayakawa et al., 1996a; Small et al., 1997a, b, 1999; Cerf-Ducastel et al., 1998, 2001; Zald et al., 1998; Frey and Petrides, 1999; Francis et al., 1999; Barry et al., 2001; O'Doherty et al., 2001; Ogawa et al., 2005) have shown taste-elicited activation in two areas corresponding to the PTA and the STA. In addition to these areas, other brain areas including the inferior part of the insula (Cerf-Ducastel et al., 1998, 2001) and the anteromedial temporal lobe (Small et al., 1997a) are also shown to be activated by taste stimuli. We have

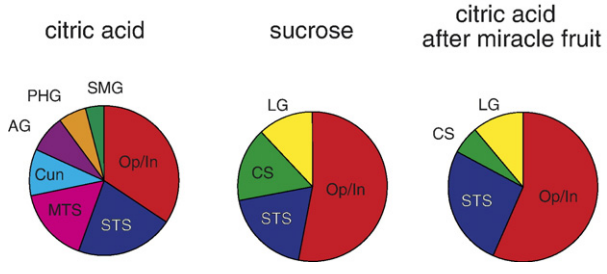

Fig. 4. Proportions of the frequency of ECDs detected during the first 1 s across cortical regions by stimulation with citric acid, sucrose, and citric acid after miracle fruit. Op/In, opercular insular cortex; CS, central sulcus; STS, superior temporal sulcus; LG, lingual gyrus; In, insular cortex; SMG, supramarginal gyrus; Cun, cuneus, MTS, middle temporal sulcus; AG, angular gyrus; PHG, parahippocampal gyrus.

shown in the present study that the PTA is localized in the operculum/insular cortex near the boundary between the frontal and parietal lobes judging from the identification of the central sulcus since the fastest taste-elicited activation was detected in this area.

The response latency in the PTA for sucrose was a few hundreds milliseconds longer than that for citric acid. This is consistent with the finding that showed that the reaction time in human adults to sucrose was about 300 ms longer than that to tartaric acid (Yamamoto and Kawamura, 1981). Since it is reported that the difference of response latency in the chorda tympani nerve for sucrose and acid is about 200–400 ms in animal experiments (Beidler, 1953; Pfaffmann and Pritchard, 1980; Harada et al., 1983), this latency difference may reflect the different transduction mechanisms between sucrose and acid, viz., sour taste transduction involves ion-channel mechanisms and sweet taste transduction involves activation of the second messenger system in taste cells (see Lindemann, 1996 for a review). Kobayakawa et al. (1996a,b, 1999) also suggested the difference between the activation latencies for NaCl and that saccharin was based on different transduction systems between the two stimuli.

The most interesting and unexpected finding in the present study was that the response latency to citric acid after miracle fruit was essentially the same as that to sucrose. As for the peripheral mechanism of taste-modifying action of miracle fruits, miraculin stimulates sweet receptors under acidic conditions, i.e., acid information is not converted to sweet information, but both acid and sweet information are conveyed through the taste nerves to the brain. This notion comes from the findings that sugar fibers are activated in addition to acid fibers in the monkey (Brouwer et al., 1983) and chimpanzee (Hellekant et al., 1998) chorda tympani nerve after treatment of the tongue with miraculin. Also after miracle fruit treatment when citric acid is reported to taste sweet in humans, sour taste is recovered by treatment of the tongue with an anti-sweet agent, gymnemic acid (Bartoshuk et al., 1974). Considering these findings, we expected to record two components of responses in the PTA corresponding to an early response to sour information and a late response to sweet information. If the sour component were to disappear as a result of processing exclusively in the cortex, the early acid responses should have been obtained in the PTA. The present results, however, showed that mainly the late response was detected (see Fig. 3), suggesting that the sour component signal in the taste nerves diminishes while being processed through the brain stem to the PTA. This explanation is plausible on the basis of the fact that interaction occurs at the brain stem gustatory relay nuclei in hamsters, i.e., mixture suppression occurs in the responses to binary mixtures of sucrose, NaCl, citric acid and quinine presented to the anterior tongue (Vogt and Smith,

1993, 1994; Smith et al., 1994). To confirm and extend the mixture effect of sweetness and sourness suggested for the action of miracle fruit, a further study should be done on the mixture effect of different tastes under well controlled design with the MEG technique in humans.

These findings also suggest that simple reception of ascending neural inputs for PTA neurons may be sufficient to induce simple and rapid sensation of the taste quality because the taste information, even in part, has been processed or modified through the subcortical taste pathway. This notion may not be different from the sensory processing for touch, temperature or pain in the somatosensory area. Cortical neurons that receive ascending labeled-line signals (Frank, 1973) may project to confined areas within the PTA to induce the sensation corresponding to the signals. Such a chemotopic organization has been suggested in rats (Yamamoto et al., 1989) and in humans (Schoenfeld et al., 2004). Although the across-neuron response pattern notion (Erickson, 1963) and temporal pattern notion (Nagai and Ueda, 1981) are also suggested as the taste quality coding theories, decoding of these patterns may require time-consuming complex modes of neural processing, which might be utilized for discrimination of subtle differences of taste quality. In this sense, there is a possibility that electrical stimulation of confined areas of the PTA induces taste sensation such as sweet, salty, sour, bitter or umami, although Penfield and Boldrey (1937) were not successful in inducing any distinct taste quality when the cortex overlying or near the PTA was stimulated with a fairly large electrode.

A series of studies by Rolls and his colleagues using electrophysiological single unit recording techniques in macaques (Rolls, 1997) and neuroimaging methods in humans (Francis et al., 1999; O'Doherty et al., 2001) have suggested that the OFC is involved in representing the affective aspects of taste. Although not stated in the results of this study, we observed possible taste-elicited activation in the OFC in two subjects. A lack of clear evidence for the MEG responses in the OFC may be due to a methodological difficulty in recording MEG activity from the rostroventral part of the forebrain as noted by Kobayakawa et al. (1999) and the inadequate affective reactions due to the short duration and small area of taste stimulation. Considering the fact that MEG responses were recorded from the OFC in different experimental paradigms (Tonoike et al., 1996; Ioannides et al., 2000; Northoff et al., 2000; Amo et al., 2004), it seems unlikely that taste-elicited MEG responses from the OFC would be detected if the taste stimuli are applied to a wider area of the tongue with a longer stimulus duration. This is one of the issues to be investigated in future MEG studies on taste.

The experience of taste is similar to the experience of pain in the sense that both sensory and affective components are involved. Fulbright et al. (2001) tried to determine areas of the brain engaged by the affective dimension of pain by fMRI. They reported that, compared with the basic sensory processing of pain, the affective dimension of pain activated a cortical network that included the right superior frontal gyrus, the right cuneus and a large area of the anterior cingulate gyrus. Their results are consistent with previous electroencephalographic studies showing right frontal activation in association with unpleasant or negative affective experiences (Spence et al., 1996; Roschmann and Wittling, 1992). It has been proposed that the right hemisphere mediates withdrawal-related behaviors, whereas the left mediates approach behaviors (Davidson, 1995). In the present taste study, we could not see any lateralized activation to affective components of sour and sweet taste except the OFC as already discussed. This may largely be attributed to the technical differences between fMRI and MEG studies, e.g., Fulbright et al. analyzed the brain activity during the painful stimulation lasting for more than 30 s, whereas we analyzed the activity for less than 1 s. During such a fairly long period of pain stimulation, brain regions with increased signal intensity could result from affective–cognitive dimensions including anticipation, subjective experience and other mental processes. In comparison, within less than 1 s of analysis time, we could detect only basic sensory and hedonic responses: the mental processes such as anticipation and subjective experiences of the taste stimuli may not be represented.

Thus, different areas may be activated by gustatory information through different ascending pathways that transmit taste information and the intracortical connections. Alternatively, activation of various parts of the brain may reflect the involvement of chemical systems influencing widespread areas of the brain by taste stimulation. Recent evidence indicates that benzodiazepine, opioid and dopamine are specifically involved in the generation of palatability and facilitation of food and fluid consumption (see Yamamoto et al., 1998 for a review). It is well known that dopaminergic fibers from the ventral tegmental area project widely to various parts of the forebrain including the cerebral cortex. Although the sites of action remain to be studied, endogenous benzodiazepine derivatives, opioids including beta-endorphin and a candidate for aversion-related substance, diazepam binding inhibitor (Manabe et al., 2000), may also directly or indirectly influence cortical activity.

In conclusion, comparing sweet and sour information conveyed by the taste nerves in response to citric acid after chewing miracle fruit, the present MEG study strongly suggests that only sweet information is processed by the primary taste area. Citric acid after miracle fruit was very similar to sucrose in terms of the response latency and the across-region response pattern of the cerebral cortex possibly representing the affective aspect of taste.

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