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Contribution of Umami Substance to Swallowing

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Abstract

Reflecting progressive aging of society, many special diets for patients suffering from swallowing disorders (i.e. dysphagia diets) have been developed. Texture modification for less risk of aspiration is one of the important elements in dysphagia diets from the viewpoint of safety assurance. However, no attempt has been done to add chemicals to such diets to facilitate swallowing initiation. For this, sensory inputs from the oropharynx play an important role in swallow initiation. Animal studies showed that stimulation by umami taste is effective stimulus of this area. Therefore, to study the effect of umami taste on swallow initiation in humans, we examined the effect of application of Monosodium L-Glutamate (MSG) solution as an umami taste to the oropharynx on the latency of the swallow reflex evoked by electrical stimulation of the oropharynx. Distilled water (DW) and 0.15 M sodium chloride (NaCl) solution (saline) were used as vehicles of MSG. Each of the DW, saline, 0.1 M MSG dissolved with DW (MSG-DW) and 0.1 M MSG dissolved with saline (MSG-saline) were slowly injected approximately 1 s prior to electrical stimulation. The amount of each solution was 0.1 ml. No swallow was evoked when each of the solutions was applied to the posterior wall of the oropharynx without electrical stimulation, and the subjects could not discriminate the solutions. Results showed that application of DW to the oropharynx shortened the latency of the swallow reflex, but saline application elongated the latency of the reflex. Also, application of MSG-saline solution counteracts the elongation of the latency induced by saline application. This counteractive effect of MSG was concentration-dependent. Above findings suggest that using MSG as a food additive with NaCl (i.e. salty taste) may serve not only as a flavor enhancer but also as an enhancer of swallow initiation.

Keywords: Swallow; Reflex; Pharynx; Taste; Glutamate; Humans

Introduction

Population aging occurs in many societies. As a result, patients suffering from swallowing disorders (i.e., Dysphagia) are increasing. Dysphagia subsequently develops serious problems such as aspiration pneumonia, suffocation, dehydration and malnutrition, which affect the patient's Quality of Life (QOL). Therefore, there is expanding social demand for the development of better rehabilitation treatment of dysphagic patients. One of the important approaches for the improvement of nutritional status and QOL of dysphagic patients is dietary management with the use of special food (i.e., dysphagia diets) [1]. Texture modification of food is one of the important elements of dysphagia diets. For example, a softened, highly aggregable food is known to help patients masticate and form a bolus of food and to reduce the risk of aspiration. Such approach to reduce the risk of aspiration is very important from the viewpoint of safety assurance. However, there is still room to develop better dysphagia diets. For example, improvement of palatability may be one of the possible approaches for the further development of dysphagia diets, since it encourages appetite and also enhances the enjoyment of food. The other may be to develop dysphagia diets that facilitate swallow initiation.

Swallowing involves several motor processes such as bolus formation and intraoral transport of a food bolus (oral stage) and a series of visceral events that occur in a relatively fixed timed sequence but are to some degree modifiable (pharyngeal stage or swallow reflex) [1-4]. Among the motor processes, the swallow reflex can be triggered by mechanical, chemical, and thermal stimulation in the oropharynx or larynx [4,5]. Particularly, the oropharynx, where chewed food is usually transported and aggregation of food bolus occurs during natural feeding, play an important role in swallow initiation [6-8]. For this, we have found that application of small amount of Monosodium L-Glutamate (MSG), which is one of the most abundant naturally occurring amino acids, frequently added as a flavor enhancer and well known as an umami taste [9,10], activates sensory fibers innervating this area in animal [11]. Recently, we also found that application of MSG dissolved with distilled water to this area increases the incidence of reflexively elicited swallows by electrical stimulation of oropharynx [12]. The finding strongly suggests that umami stimulation of the oropharynx facilitates the initiation of the swallow reflex. However, we cannot deny the possibility that the effect of umami solution was due to the vehicle (water), which is already known to be a major chemical stimulant of this area and an initiator of the swallow reflex [13,14]. To clarify this, we examined whether application of MSG solution dissolved with saline as well as distilled water to the oropharynx modulates the initiation of the swallow reflex.

Materials and Methods

Subjects

Six healthy volunteers (25-46 years old; 6 males) without swallowing disorders were enrolled in this study. The experimental protocol was approved by the Ethics Committee of Niigata University Graduate

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School of Medical and Dental Sciences. The purpose of this study was fully explained to the subjects, and written informed consent was obtained from each participant prior to initiating the experiments.

Recordings

The subjects sat relaxed in an experimental chair in a neutral posture with the backrest adjusted. A pair of surface electrodes (Ag/AgCl, 5 mm in diameter; NT-611T, Nihon Kohden Corp) was placed on the skin to record swallow related electromyographic (EMG) activity of the suprahyoid muscles. Swallows were identified by the visual observation of larynx movement and by the EMG burst of the suprahyoid muscles. In addition, subjects were asked to push a switch button when they recognized the act of swallowing, and the signal from the switch button was recorded. Respiratory movement was also measured at the chest using tension sensor placed around the chest.

Electrical stimulation

The methods for eliciting reflex swallows by electrical stimulation of the pharyngeal wall in man have been detailed [15] and so only a brief description follows. A custom-made monopolar silver stimulating electrode tip (2 mm in diameter and 10 mm long) welded to an insulated stainless-steel coil spring tube was used to elicit reflex swallows. The stainless-steel coil spring tube and a polyethylene tube (0.58 mm in internal diameter and 0.97 mm in external diameter) were inserted in a silicon tube (1.40 mm in internal diameter and 2.35 mm in external diameter) (Figure 1A). The tip of the polyethylene tube was set at the weld of the electrode tip and the coil spring tube. Then the silicon tube were introduced into the pharyngeal region through the nasal cavity, and placed on the posterior wall of the oropharynx (Figure 1B), and the electrode tip was fixed on the lateral posterior wall of the oropharyngeal region. These operations were performed with the help of a guide wire inserted in the coil spring tube.

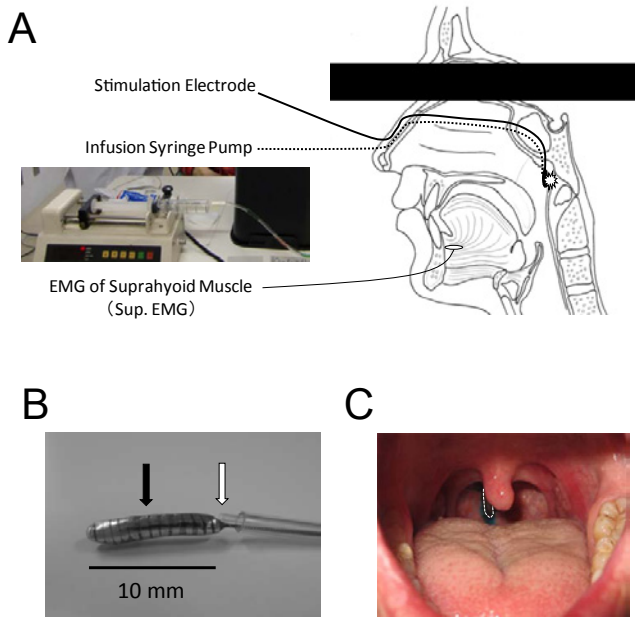

Figure 1: The experimental setup. **A:** Diagrammatic illustration of the system stimulating the oropharynx by electric pulses (stimulation electrode), and by test solutions (infusion syringe pump) in humans. Both stimulus apparatus tube were introduced into the pharyngeal region through the nasal cavity, and placed on the posterior wall of the oropharynx. See text for details. **B**: Enlarged picture of the electrode tip (filled arrow) connected to a flexible stainless-steel coil spring tube for electrical stimulation and tip of the polyethylene tube for stimulation by solution (open arrow). **C**: Position of the electrode on the posterior wall of the oropharynx and the area stimulated by a test solution. The electrode is indicated by dashed line, and the area after application of a test solution (0.1 ml) is stained blue with food coloring.

Next, repetitive electrical pulses (0.8 mA, 1 ms duration at 30 Hz, at most for 15 s) were applied to the oropharyngeal mucosa by an electric stimulator (SEN-3301, Nihon Kohden Co. Ltd., Tokyo, Japan) through a stimulus isolator (SS-202J, Nihon Kohden Co. Ltd.). The initial intensity of electrical current was 0.8 mA. When a swallow was evoked within 1.5 s, the current intensity was decreased by 0.1 mA step and the reflex threshold was determined. In this study, the reflex threshold was determined as the lowest electrical current from which the swallow reflex was evoked within 1.5 s. If no swallow was evoked at the intensity of 0.8 mA, the subject was instructed to open his/her mouth to allow visual confirmation of the electrode position by the experimenters, and the position of the electrode tip was adjusted until the swallow reflex was evoked by the current less than 0.8 mA. These procedures were common in the following two experimental sessions.

Stimulation with umami solution

Experiment 1: After the determination of the reflex threshold, the intensity of electrical stimulation of oropharynx was set at 1.5 T of the threshold. Then the electrical stimulation alone was applied to oropharynx for 15 s, and the latency for the first evoked swallow was measured. This procedure was repeated three times, and the mean latency was calculated and defined as pre-control. Next, one of the following test solutions was applied to the oropharynx in addition to 15 s electrical stimulation. Test solutions were distilled water (DW), 0.15 M sodium chloride (saline), 0.1 M Monosodium L-Glutamate (MSG: umami taste) dissolved with DW (MSG-DW) and 0.1 M MSG dissolved with saline (MSG-saline). The amount of each solution was 0.1 ml and injected approximately 1 s prior to electrical stimulation. The rate of the injection was set at 0.4 ml/min using electrically driven infusion syringe pump (Figure 1C). Application of each solution with electrical stimulation was consecutively repeated three times with 180 s interval. The subject was asked to drink approximately 10 ml of water at the end of each stimulation trial to reduce dryness of the mouth and to avoid contamination of the solutions. The order of the solution and the timing of stimulation were blind for the subjects. After testing all test solutions, the electrical stimulation alone was again applied three times to the oropharynx and the mean latency for the reflex was calculated (post control). If the mean latencies of pre- and post-control were different more than 0.3 s, all the session was omitted. Each subject underwent above session daily and at least two sessions in total. These experimental procedures are illustrated in Figure 2.

Experiment 2: Since the MSG-saline application was effective on the reflex latency (see results), saline and three different concentrations (0.01 M, 0.1 M and 0.3 M) of MSG-saline solutions were applied with electrical stimulation to the oropharynx to verify whether the effect was concentration-dependent. After the determination of the reflex threshold, the intensity of electrical stimulation of oropharynx was set at 1.5 T of the threshold and the electrical stimulation alone was applied and pre-control value was obtained. Then, one of saline or MSG-saline solutions with different concentrations was applied with electrical stimulation. Application of each solution was consecutively repeated three times with 180 s interval. Remaining procedures were conducted in the same way as described for the experiment 1.

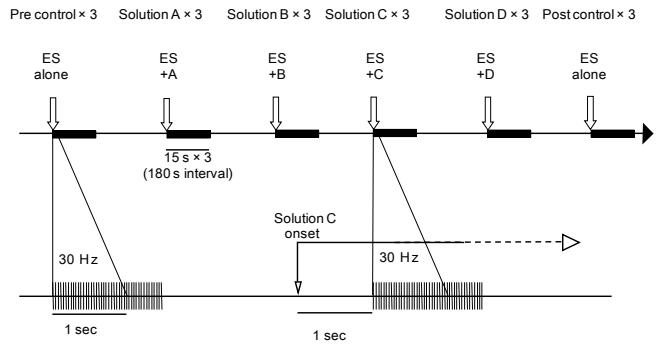

Figure 2: Schematic illustration of the experimental protocol. At the beginning of each session, the threshold (T) of the swallowing reflex is determined. Then electrical stimulation alone (ES alone) was applied to oropharynx for 15 s. This procedure was repeated three times with 18 s interval, and the mean latency was calculated and defined as pre-control. Then one of the test solutions was applied to the oropharynx in addition to 15 s electrical stimulation (ES+A). The test solution was injected approximately 1 s prior to electrical stimulation. This procedure was also repeated three times with 18 s interval, and other solutions were also tested in the same manner (ES+B, ES+C and ES+D). After testing all test solutions, the electrical stimulation alone was again applied three times to the oropharynx (ES alone), and the mean latency for the reflex was calculated as post control.

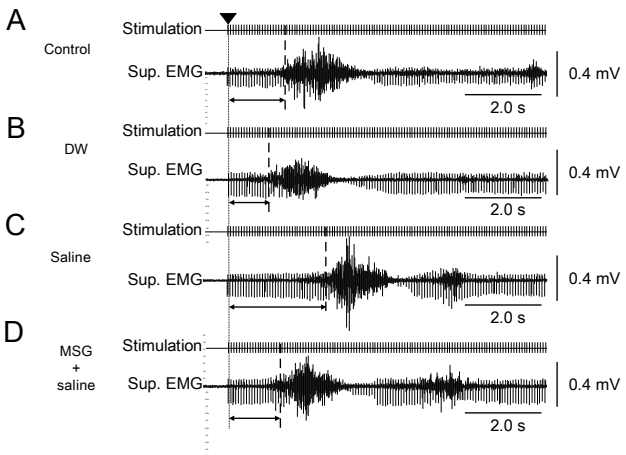

Figure 3: Typical samples of EMG recordings from the suprahyoid muscle of evoked swallows during electrical stimulation to the oropharynx alone (A: Control), electrical stimulation with distilled water (B: DW), electrical stimulation with 0.15 M NaCl and (C: Saline) and electrical stimulation with 0.1 M monosodium L-glutamate (MSG: umami taste) dissolved with 0.15 M NaCl (D: Saline+MSG). Each of the recordings, upper trace illustrates electrical stimulation pulses (stimulation) and lower illustrates swallow-related EMG activities of the suprahyoid muscle (Sup EMG). The down-pointing triangle and vertical dotted line indicate the onset electrical stimulation. The vertical dashed line in each of the recordings indicates the onset of the swallow reflex and thereby the double-headed arrow indicates the latency in each of stimulus conditions.

Analyses

Suprahyoid EMG activities were amplified with AC amplifiers (band pass: 0.1-3 kHz), and the signals were fed into a computer equipped with a CED Power 1401 board and analysis software (Spike2; Cambridge Electronic Design Ltd., Cambridge, UK). The sampling rate for the EMGs was 5000/s. The stimulus pulses for the test stimuli were also fed into a computer with a CED Power 1401 board as event signals.

The onset of the reflex latency was defined as the time from stimulus onset to the first evoked swallow. To define the onset of each reflex, the baseline EMG activity in the suprahyoid muscle was calculated for 2 min during the control period, and the onset was defined as the time point when swallow-related EMG activity exceeded 2SD from baseline EMG activity.

Effects of application of each of the test solutions on the swallow reflex were statistically evaluated with a repeated measures one-way ANOVA and post-hoc comparisons (Tukey test). A paired t-test was used for the comparison of the control reflex latency between the experiment 1 and 2. The values were expressed as mean +/- SD, and P values less than 0.05 were regarded as significant.

Results

Swallow reflex evoked by electrical stimulation

The threshold of the swallow reflex evoked by electrical stimulation of the posterior wall of the oropharynx was 0.57 +/- 0.23 mA (n=6) for the experiment 1 and was 0.42 +/- 0.17 mA (n=6) for the experiment 2. Mean latency of the reflex at the 1.5 T of the threshold was 0.75 +/- 0.09 s (n=6) for the experiment 1 and was 0.68 +/- 0.09 s (n=6) for the experiment 2. Both the thresholds and latencies were not significantly different between the experiments (p>0.05, paired t-test). The subjects recognized the timing of electrical stimulation and reported that stimulation did not create pain sensation.

Effect of taste stimulation on the swallow reflex evoked by electrical stimulation of the oropharynx

No swallow was evoked when each of the solutions (i.e. DW, saline,

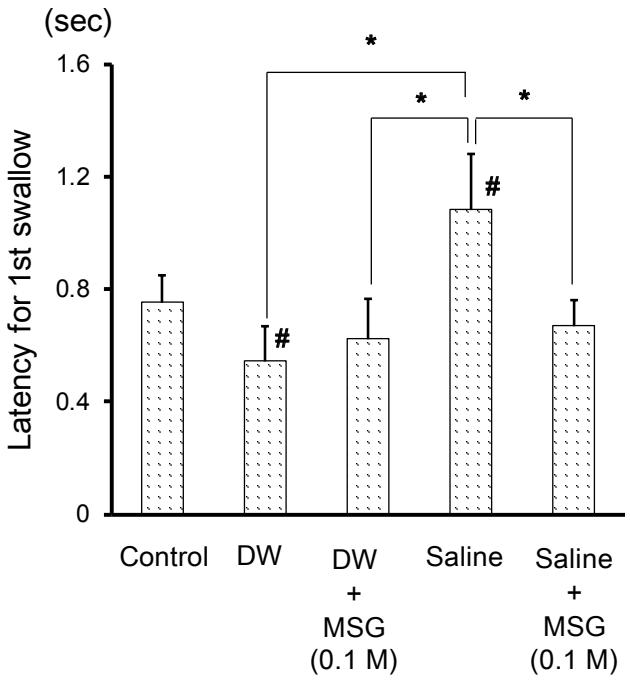

Figure 4: Effect of stimulation of oropharynx by test solutions on the latency of the swallow reflex evoked by electrical stimulation of the oropharynx. Results were shown as mean ± S.D.
#indicates a significant difference was noted when the value was compared to control (P < 0.05, Repeated measures one-way ANOVA and post-hoc Tukey test, n=6).
*indicates a significant difference between the values (p < 0.05, Repeated measures one-way ANOVA and post-hoc Tukey test, n=6). Abbreviations are the same as in Figure 3. See text for details.

MSG- DW and MSG-saline) was applied to the posterior wall of the oropharynx without electrical stimulation in all subjects. Also, the subjects could not discriminate the above solutions during experiment.

Figure 3 shows examples of raw data and figure 4 shows the mean latency of the swallow reflexes evoked by electrical stimulation of the oropharynx alone (control) or by electrical stimulation with test solutions. The latency of the reflex was 0.54 +/- 0.12 s when DW was applied together with electrical stimulation, and the value was significantly smaller than the latency when electrical stimulation alone was applied (0.75 +/- 0.09 s: control) ($p<0.05$, one-way repeated measures ANOVA and post-hoc Tukey test, n=6, Figures 3A and B). On the contrary, the reflex latency was significantly elongated (from 0.75 +/- 0.09 s to 1.08 +/- 0.20 s) than control when saline was applied together with electrical stimulation ($p < 0.05$, one-way repeated measures ANOVA and post-hoc Tukey test, n=6, Figure 3C). When MSG-saline was applied, the latency of the reflex was 0.67 +/- 0.09 s, and the value was significantly smaller than the latency when saline was applied ($p < 0.05$, one-way repeated measures ANOVA and post-hoc Tukey test, n=6, Figure 3D). No significant difference was noted between the control and MSG-saline. The latency of the reflex was 0.62 +/- 0.14 s when MSG-DW was applied, and the value was also significantly smaller than the latency when saline was applied but was not significantly different from control ($p < 0.05$, one-way repeated measures ANOVA and post-hoc Tukey test, n=6).

To verify whether the counteractive effect of MSG on the elongation of the latency of the swallow reflex induced by saline application were mediated in a concentration-dependent manner, we tested the reflex latency when MSG with a range of concentrations (0.01-0.3M) dissolved with saline was applied together with electrical stimulation of the oropharynx (Figure 5). Mean latency of the reflex at the 1.5 T of the threshold was 0.68 +/- 0.09 s (n=6). The latency was significantly elongated to 1.02 +/- 0.18 when saline was applied with electrical stimulation ($p < 0.05$, one-way repeated measures ANOVA and post-hoc Tukey test, n=6). Application of 0.01 M MSG with saline did not affect the elongation effects of the reflex latency induced by saline but application of 0.1 or 0.3 M MSG shortened the latency to the control level. The mean latency was shorter for 0.3 M MSG than for 0.1 M MSG, although the values were not significantly different.

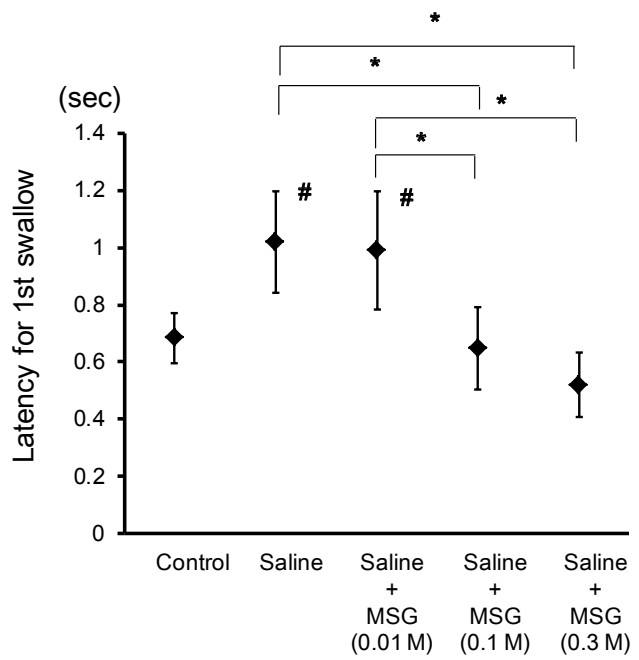

Figure 5: Effect of MSG concentration on the elongation of the swallow reflex induced by application of saline. Results were shown as mean ± S.D.
#indicates a significant difference was noted when the value was compared to control ($P < 0.05$, Repeated measures one-way ANOVA and post-hoc Tukey test, n=6).
*indicates a significant difference between the values ($p < 0.05$, Repeated measures one-way ANOVA and post-hoc Tukey test, n=6). Abbreviations are the same as in Figures 3 and 4, and concentrations of MSG are in the parentheses. See text for details.

Discussion

The present study showed that application of DW to the oropharynx enhances the initiation of the swallow reflex evoked by electrical stimulation of the oropharynx, but saline application suppresses the initiation of the reflex. Also, application of MSG solution as umami taste counteracts the suppressive effects of swallow initiation induced by saline.

Technical considerations

It is now well established that the initiation of the swallow reflex depends on the activity of brainstem neurons that belong to a functionally defined swallowing center or swallowing Central Pattern Generator (CPG) [16,17,18]. However, considerable evidence suggests that the cerebral cortex may also play an important role in the initiation and regulation of swallowing [19-25]. We also found that emotional and behavioral states sometimes overcome other modulatory effects on swallow initiation in the case of humans [12,15]. It is likely that swallow initiation is affected if the subjects recognized the taste of the test solutions and felt some emotions. In this aspect, it should be noted that the subjects did not feel any taste of the solutions applied to the oropharynx during experiment. This indicates that modulatory effects of the test solutions observed in the present study was not caused by higher brain function (e.g. cognitive function) but rather by reflex function.

Effect of electrical stimulation to the oropharynx on swallow initiation

The oropharynx is innervated by the pharyngeal plexus, which is identical to the pharyngeal branch of the GPN (GPN-ph) in animals, and plays an important role in swallow initiation. Sensory information from this area is sent to the nucleus of the solitary tract (NTS), where the dorsal neuron group of the swallowing center triggering the swallowing reflex exists [16]. Effective stimuli eliciting the swallow reflex of this area are mechanical, chemical, and thermal stimulation. It was notable that no pain sensation was created by electrical stimulation of the oropharynx, indicating that thin sensory fibers (e.g. A delta and C fibers) responding to noxious stimulation were not activated by the stimulus intensity used in the present study. This in turn suggests that major sensory fibers activated by electrical stimulation of oropharynx were relatively large fibers (e.g. A beta fibers) innervating mechanoreceptors of the oropharynx. However, many subjects reported that sensations related to water were created by electrical stimulation. This suggests that electrical stimulation to the oropharynx also activated sensory fibers responding to water stimulation of this area, at least partly.

Effect of application of solutions to the oropharynx

It was also notable that no swallow was evoked when each of the solutions was applied to the oropharynx without electrical stimulation.

The rate of the injection was 0.4 ml/min, and the value is close to the rate of unstimulated saliva [26] to minimize the mechanical effect of infusion. In addition, we have recently tested the effect of the stimulus frequency of electrical stimulation of pharynx on the latency of the swallow reflex, and showed that the latency became shorter as the stimulus frequency increased up to ≤ 30 Hz, but no further reduction in the latency was observed at the frequency exceeded 30 Hz [15]. The stimulus frequency used in the present study was 30 Hz, which indicates sensory inputs to the swallowing center from mechanoreceptors were almost saturated by electrical stimulation. Therefore, the mechanical effect of infusion of solution could be neglected in the present experimental condition, and thereby a chemical effect such as taste on the swallow reflex was observed by application of solutions.

Sensory inputs from the GPN-ph have unique responses to taste stimulation which differ from responses of the chorda tympani nerve and lingual branch of the GPN. Our previous study conducted in animal showed that water evokes a robust response in the GPN-ph. On the contrary, application of NaCl (i.e. salty taste) at physiologic concentrations attenuates the water response [11]. Such response characteristic is consistent with that of the superior laryngeal nerve, which is known to be another important sensory nerve in the swallow initiation [27]. These findings are consistent with the present finding that application of DW to the oropharynx enhanced the initiation of the swallow reflex. Such facilitatory effect of water stimulation to the pharyngeal region on swallow initiation has also been reported by others, showing that application of water to the laryngopharynx shortened swallowing intervals in repetitive voluntary swallowing in humans [13,14]. They also showed that application of 0.3 M NaCl solution prolonged swallowing intervals, and suggested that the action of NaCl is inhibition of water response [14]. The present result showing the suppression of swallow initiation by application of saline (0.15 M NaCl) may partly support their idea. However, if the action of NaCl is only a simple inhibition of water response, the elongation of the latency can be explained only by the inhibition of possible water fibers that was already activated by electrical stimulation. It is possible that application of NaCl produced some inhibitory effects on the swallowing center.

Effect of umami stimulation to the oropharynx

The action of umami (MSG) at the pharynx has been tested only by us. We found that the GPN-ph respond to solutions of umami taste (MSG) applied to the pharynx in mice [11]. This finding suggests that application of MSG increases sensory inputs to the swallow center and acts as a facilitator for swallow initiation. The present results conducted in humans showing that application of MSG solution counteracts the suppressive effects of swallow initiation induced by saline support the view that MSG is a facilitatory factor of swallow initiation at the oropharynx. Interestingly, however, the facilitatory effect did not exceed that of water. Such modulatory pattern at the GPN-ph was observed in rats [11]. So the action of MSG on the sensory receptors may be different between the animals. Neural mechanisms underlying the responsiveness of sensory fibers to MSG as well as interactions between MSG, NaCl and water at the pharynx are still unknown. For this, it is unlikely that the effect of MSG showing reduction of the swallowing latency due to saline is due to an increased concentration of sodium ion from MSG, not from the presence of glutamate, since Kitada et al. showed that stimulation of similar area by NaCl (0-0.3 M) solution suppresses swallow initiation in a dose-dependent manner in humans. However, we still do not know what kind of glutamate receptor is responsible for the sensory activity induced by application of MSG to the pharynx. In the tongue, it is reported that MSG has multiple receptor systems such as metabotropic-type glutamate receptors (mGluR1 and mGluR4) as well as T1R1/T1R3 in the taste organs [28]. Also, non-N-methyl-D-aspartate (non-NMDA) type postsynaptic receptors are suggested to contribute glutamatergic efferent regulation of taste organs [29]. However, taste organs responding to MSG has not been identified in the pharynx so far. Instead, there is considerable evidence that N-Methyl-D-Aspartate (NMDA)-type glutamate ion channel receptor responds to MSG, and NMDA-type glutamate ion channel receptor exists not only in the taste cells [30,31] but also in the peripheral nerve endings conveying somatic sensation [32]. The finding is consistent with the present finding that the subjects did not feel any tastes of the solutions applied to the oropharynx during experiment and suggests that NMDA or other glutamate ion channel receptors play a role for the modulation of swallow initiation observed in the present study. For this, further study will be needed.

Functional implications

In the natural feeding behavior, the swallow reflex occurs following the oral stage, in which many kinds of cognition definitely occur. As discussed above, emotional and behavioral states based on the cognitive functions play an important role on swallow initiation in the case of humans. Therefore, we cannot conclude that diets containing umami substance enhance swallow initiation. However, it is likely that perception of umami taste (MSG) is also a factor facilitating swallow initiation, since it improves the taste of foods [33], and encourages appetite and mastication in most case [34]. In addition, umami stimulation improves saliva secretion and helps aggregate food bolus particularly in elderly suffering from hyposalivation [9]. Improvement in the palatability of the food and its perception may also lead to facilitatory inputs from higher brain to the swallowing center.

On the other hand, NaCl as a salty taste may be a factor suppressing swallow initiation at the oropharynx by the suppression of the water response, although previous study showed that it may facilitate swallow initiation when applied to the posterior tongue [13]. Together with above findings, using MSG as a food additive may serve not only as a flavor enhancer but also as an enhancer of swallow initiation, although further study will be needed to clarify whether the MSG can cause the same effect against NaCl in the elderly.

Acknowledgments

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