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Effect of Stimulation of the Laryngopharynx with Water and Salt Solutions on Voluntary Swallowing in Humans: Characteristics of Water Receptors in the Laryngopharyngeal Mucosa

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Abstract

Stimulation of water receptors in the laryngopharynx (LP) with water facilitates voluntary swallowing in humans. Based on measures of swallowing intervals (SIs) in repetitive swallowing, we investigated characteristics of laryngopharyngeal water receptors in humans. Healthy adult volunteers were instructed to perform repetitive swallowing as quickly as possible during infusion of a solution into the LP. Infusion of water shortened SI, suggesting that water excites water receptors. Infusion of 0.3 M NaCl solution prolonged SI, suggesting that the NaCl solution inhibits activity of water receptors. SI increased with increasing concentration of NaCl. Anion or cation substitutions indicated that excitation of water receptors is due to absence or reduced concentration of Cl^-. With diminution of peripheral inputs, cortical inputs would play a dominant role in voluntary swallowing. With infusion of a nonstimulating solution (0.3 M NaCl at 0.2 mL/min), SI varied greatly from subject to subject, suggesting that the ability of central regulation of swallowing to initiate repetitive voluntary swallowing varies among subjects. Facilitation of swallowing by chemosensory inputs from water receptors appeared strongly in subjects with longer SI with infusion of the nonstimulating solution. It appears that chemosensory activation compensates for the difficulty in initiating swallowing via the central neural mechanism.

Key words: human, laryngopharynx, swallowing, taste stimulus, water receptors

Introduction

Swallowing consists of a reflex sequence of muscle contractions that propels ingested materials and pooled saliva from the mouth to the stomach. Swallowing simultaneously serves to protect the respiratory tract from aspiration. Swallowing can be initiated either voluntarily or reflexively (Miller 1982). Both inputs from the cerebral cortex and sensory inputs from mucosal receptors in the oropharynx can regulate the activity of the swallowing central pattern generator (CPG) located in the medulla oblongata and the CPG can trigger swallowing (Jean 2001; Ertekin and Aydogdu 2003). Therefore, there might be interactions between sensory and cortical inputs for initiation of swallowing. However, the interaction between the 2 mechanisms has not been fully elucidated.

A reflexogenic area readily eliciting swallowing is the laryngopharynx (LP). Mechanical and chemical stimulation of the LP can evoke reflex swallowing (Miller 1982). It has been found that water applied to the LP induces reflex swallowing in animals such as cats (Miller and Sherrington 1916; Storey 1968a, 1968b; Ootani et al. 1995), rabbits (Shingai and Shimada 1976), and rats (Kijima et al. 2006). This swallowing reflex elicited by water is dependent on water-sensitive fibers (water fibers) in the superior laryngeal nerve (SLN) of the vagal nerve (Storey 1968a, 1968b; Shingai 1977). In general, excitation of water-sensitive receptors (water receptors) in the SLN is inhibited by hypertonic NaCl solution (Bradley 2000). The inhibition of activity of water receptors

by NaCl is due to Cl^- in rabbits (Shingai 1977) and puppies (Boggs and Bartlett 1982), whereas Cl^- is not a crucial factor for inhibition of water response of water receptors in cats (Stedman et al. 1980) and rats (Shingai 1980). Therefore, excitation of water receptors involves a diversity of mechanisms. Although taste receptor proteins triggering signal transduction events were identified by means of electrophysiology, molecular biology, genetic approaches, and also screening the mass of genome sequence data (Chandrashekar et al. 2006; Sugita 2006), molecular mechanism of excitation of water receptors remains elusive.

Although water applied to the throat has been used to induce swallowing reflex in humans (Hughes and Wiles 1996; Ertekin et al. 2001), there are only a few reports on characteristics of water receptors. In humans, Shingai et al. (1989) measured the latency of reflex swallowing induced by application of water or salt solutions to the throat. They showed that water was the most effective stimulus for elicitation of swallowing reflex. Stimulation with solutions of various concentrations of NaCl affected the latency, but their effects were complicated because salt solutions above 0.05 M stimulated salt taste receptors in the posterior tongue (PT). Recently, we were able to stimulate water receptors in the LP in humans without stimulation of salt taste receptors in the PT even though a hypertonic saline solution was used as a stimulant (Yahagi et al. 2008). That is, solutions were infused into the LP through a fine tube inserted into the LP orally during voluntary swallowing. Repetitive voluntary swallowing makes it possible to withdraw the infused solution from the LP quickly and thereby the solution could stimulate only a limited area of the LP in which water receptors are located. Infusion of water or salt solutions into the LP affected swallowing interval (SI) in repetitive voluntary swallowing. Thus, changes in SI during stimulation of the LP with water or salt solutions may yield an indirect measure of changes in the activity of water receptors.

In this study, we measured SI in repetitive voluntary swallowing in humans during stimulation of the LP with water or salt solutions using the method described in our previous paper (Yahagi et al. 2008). The aims of the present study were: 1) to characterize the ionic activation of water receptors in the LP in humans and 2) to evaluate the role of chemosensory inputs from water receptors in voluntary swallowing.

Materials and methods

Human subjects

Eight healthy volunteers (3 males and 5 females; mean age, 36 years; range, 26–59 years) without oropharyngeal disorders, taking no medication, and without impairment of taste or olfaction were enrolled in this study. The study protocol was approved by the Ethical Committee of the School of Dentistry of Iwate Medical University. This work was done in the School of Dentistry of Iwate Medical University.

Stimulation

The experimental procedure and methods were almost the same as those described in a previous paper (Yahagi et al. 2008). The LP stimulation consisted of infusion of water (distilled water) or salt solutions thorough a fine silicone tube of 1 mm in outer diameter (94-0451-4, Sansyo) inserted into the throat orally. Water and 0.05–0.3 M NaCl solution dissolved in distilled water were chosen as infused solutions because water stimulates water receptors and because NaCl solutions inhibit the activity of water receptors. Solutions of 0.3 M Na acetate (NaAc) and 0.3 M KCl were also prepared in distilled water. These salt solutions were chosen to investigate ionic specificity of water receptors. The solutions were used at room temperature (20–25 °C). The pH of distilled water, 0.3 M NaCl and 0.3 M KCl was 5.7. The pH of 0.3 M NaAc was 8.6. Thus, solutions used in this study were not the extreme acidity or alkalinity. The tip of the tube was positioned at a distance of 12 cm from the mandibular incisors. So far we have referred to the pharyngeal region as the position of the tip of the tube at a distance of 12 cm from the mandibular incisors (Yahagi et al. 2008). In this study, we confirmed the position of the tip of the tube by transnasal video endoscopic observation. The tip of the tube at a distance of 12 cm was located within the LP (from the hyoid bone to the lower border of the cricoid cartilage). Infusion of 0.3 M NaCl into the LP did not give rise to a salty taste. However, if the tip of the tube was moved to the PT, a distance of 8 cm from the mandibular incisors, infusion of 0.3 M NaCl gave rise to a salty taste. Thus, infusion of 0.3 M NaCl was used to assess the regional distribution of the stimulant. That is, if infusion of a small amount of 0.3 M NaCl into the region at 12 cm does not give rise to a salty taste, the stimulant would be distributed in the LP. When the tip of the tube had been positioned at 12 cm, the tube was taped to the chin. Solutions were delivered through the tube using an infusion pump (SP100i, WPI). In our pilot experiments, we found that mechanical stimulation caused by infusion of solutions to the LP predominantly contributed to facilitation of swallowing when infusion rate was high (5 mL/min). To minimize the mechanical effect of infusion, solutions were delivered at a very slow infusion rate (0.2 mL/min). In this case, facilitation of swallowing caused by water stimulation clearly appeared. The infusion rate used in this study was close to the flow rate of resting submandibular saliva (0.26 mL/min; Dawes 1974). During insertion of a tube, gagging and coughing were not elicited in any subjects.

Procedure

During the experiments, each subject sat upright on a chair. At the beginning of each session, a 3-min period was allowed for the subject to become accustomed to the tube. The subjects were instructed to perform repetitive swallowing as quickly as possible after the onset of infusion. Before experiments were initiated, the subjects practiced swallowing

several times using water. During each infusion, swallowing was carried out for 1–2 min. Between trials (infusions), the subjects were told to drink water as they wished, and the next stimulation was performed after a minimum interval of 3 min. The tube position was rechecked every several infusions. Submental electromyographic (EMG) activity was recorded using 2 Ag-AgCl electrodes taped under the chin and was displayed on a thermal array recorder (RTA-1200; Nihon Kohden). Time of actual swallowing was marked concomitantly with EMG recording by asking subjects to press a button just after swallowing (Figure 1). SIs between peaks of 2 consecutive EMG bursts marked by dots showing actual swallowing were measured. Several SIs after the beginning of swallowing were discarded because of the potential influence of residual saliva on SI. The mean of 5 continuous SIs was obtained in each infusion (Figure 1A). Three trials were performed with each stimulus type for each subject and mean of SIs in 3 trials was used for analysis. The order of infusion of stimulus solutions was randomized. The subjects were not informed of the nature of the stimulus and they could not observe the activities of the investigators.

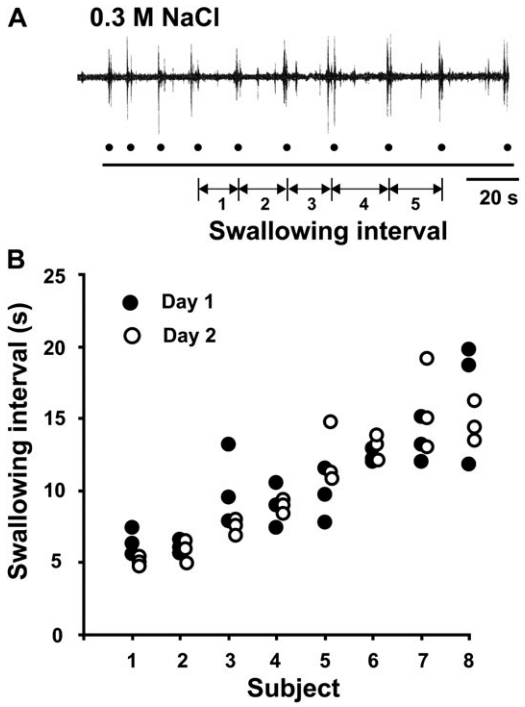

Figure 1 Measurement of SI during voluntary swallowing. **(A)** Submental EMG recording during voluntary swallowing with infusion of 0.3 M NaCl at a very slow infusion rate (0.2 mL/min) into the LP through a fine tube. The infusion of solution is indicated by a line beneath the EMG recording. Each subject was instructed to perform repetitive swallowing as quickly as possible just after the start of infusion. Dots beneath each EMG recording indicate the occurrence of actual swallowing recorded by the subject pressing a button just after swallowing. SIs between peaks of 2 consecutive EMG bursts marked by dots were measured. Several SIs after the beginning of swallowing were discarded because of the potential influence of residual saliva on the SI. Five continuous SIs were measured and the mean of the 5 SIs was obtained in each infusion. **(B)** High intraindividual reproducibility of SI and considerable interindividual variation in SI in voluntary swallowing. For each subject, SIs with infusion of 0.3 M NaCl at a very slow infusion rate (0.2 mL/min) were measured in 3 trials (infusions) on the same day. Solid circles and unfilled circles indicate SIs obtained on day 1 and day 2 (several days later after experiments on day 1), respectively. The ordinate indicates 8 subjects (numbers 1–8) who were arranged in increasing order of the magnitude of SI. Further details can be found in the text.

Statistical analysis

Paired Student *t*-test, factorial analysis of variance (ANOVA) and repeated-measures ANOVA were used for statistical analysis, and level of significance was set at $P < 0.05$. Values are presented as means ± standard error of the mean (SEM).

Results

Figure 1A shows a typical example of submental EMG recordings with infusion of 0.3 M NaCl into the LP at a very slow infusion rate (0.2 mL/min) during repeated voluntary swallowing at maximum frequency. As shown in Figure 1A, 5 continuous SIs were measured and the mean of 5 SIs was obtained in each trial. To assess the reproducibility of SI measurement, data obtained on separate days with infusion of 0.3 M NaCl were compared in each subject (Figure 1B). Three trials were performed on the same day. These data were arranged in increasing order of the magnitude of SI for 8 subjects (Figure 1B). As shown in Figure 1B, variance of SI indicated greater variation from subject to subject than from trial to trial within the subject. Statistical analysis using factorial ANOVA showed significant difference between subjects ($F_{7,32} = 24.690$, $P < 0.0001$) but not between days ($F_{1,32} = 0.042$, $P = 0.8384$). The results shown in Figure 1B showed high intraindividual reproducibility of SI for each subject. Thus, the value of SI was determined by the mean of SIs in 3 trials for each stimulus type in the following sessions.

Infusion of water into the LP shortened SI and infusion of 0. 3 M NaCl prolonged it as previously reported (Yahagi et al. 2008). In the present study, SIs with infusion of NaCl solution were measured in a wide concentration range from 0 (water) to 0.3 M. Dose-SI curves for NaCl for 8 subjects are presented in Figure 2A. Although considerable interindividual variation in SI was observed at a given concentration of NaCl, SI increased with increasing concentration of NaCl for all subjects. The individual data points are averaged in Figure 2B. Statistical analysis using ANOVA with repeated measures showed significant effects due to NaCl concentration ($F_{5,35} = 20.067$, $P < 0.0001$). Because prolongation of SI by NaCl is thought to be due to inhibition of the activity of water receptors, the dose-SI curve for NaCl implies inhibition of the activity of water receptors by NaCl in a dose-dependent manner.

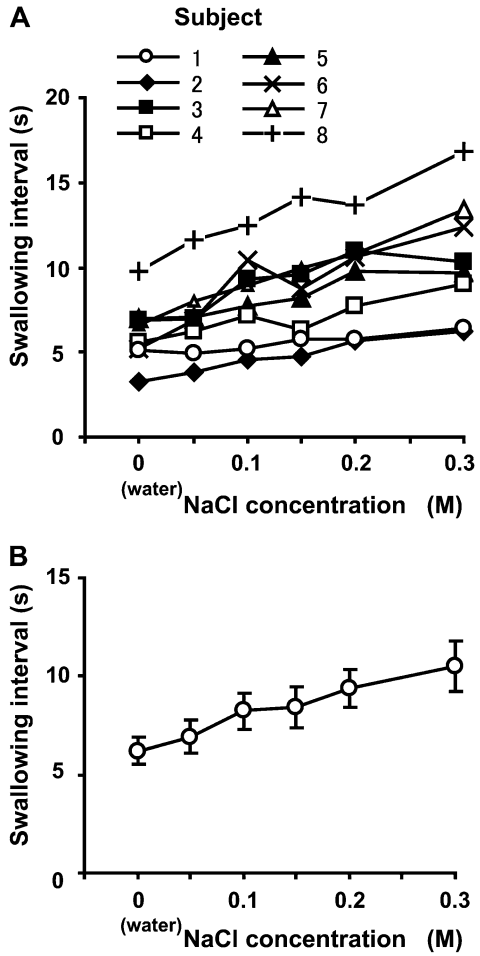

Figure 2 Dose-SI curves for NaCl. **(A)** SIs are shown for infusion of NaCl of varying concentrations at 0.2 mL/min into the LP. The order of infusion of stimulating solutions with different concentrations of NaCl was randomized. Symbols represent 8 different subjects. Each subject number corresponds to the subject number shown in Figure 1B. Each point represents the mean value of SIs in 3 trials. **(B)** Means and standard errors for data in (A). Note that SI increased with increasing concentration of NaCl.

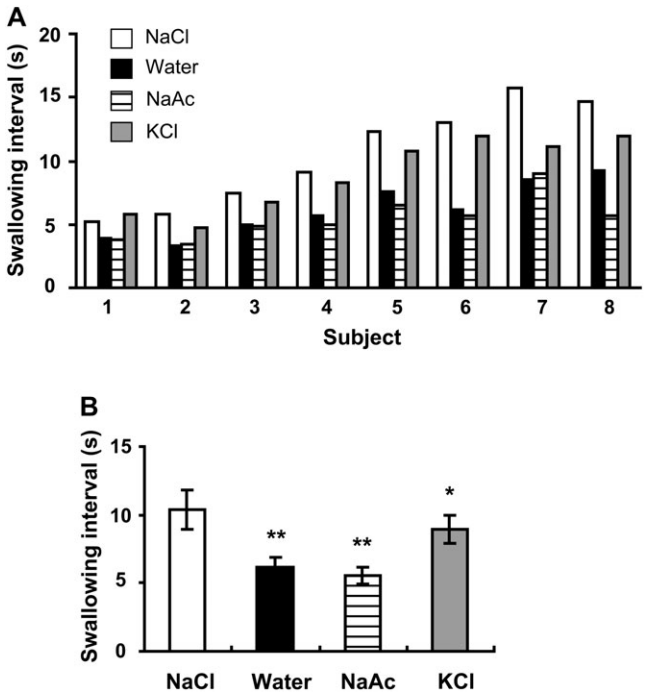

Figure 3 Effects of infusion of water and salt solutions on SI during voluntary swallowing. **(A)** SIs are shown for infusion of water, 0.3 M NaCl, 0.3 M Na acetate (NaAc), and 0.3 M KCl at 0.2 mL/min into the LP for 8 subjects. The order of infusion of stimulus solutions was randomized. Each subject number corresponds to the subject number shown in Figure 1B. Each value represents the mean value of SIs in 3 trials. **(B)** Means and standard errors for data in (A). $*P < 0.05$; $**P < 0.01$ versus 0.3 M NaCl. Note that infusion of chloride salts (NaCl and KCl) prolonged SI and that infusion of solutions in the absence of Cl^- (water and NaAc) shortened SI. Further details can be found in the text.

To test the relative importance of Cl^- or Na^+ for prolongation of SI by NaCl, Cl^- ions were replaced by acetate ions, and Na^+ ions were replaced by K^+ ions. Figure 3A shows SIs with infusion of 0.3 M NaCl, water, 0.3 M NaAc, and 0.3 M KCl for 8 subjects. Data were arranged in according to subject number as shown in Figure 1B. In all subjects tested, there was a similar chemical specificity of initiation of swallowing under volitional effort. Means for these data are presented in Figure 3B. SI was shorter in the case of infusion of water or 0.3 M NaAc than in the case of infusion of 0.3 M NaCl or 0.3 M KCl ($P < 0.01$). The difference between SIs with infusion of water and with infusion of 0.3 M NaAc was not statistically significant ($P > 0.05$). The results indicated that osmolarity was not a critical factor for initiation of swallowing. Infusion of 0.3 M KCl caused only a small reduction of SI compared with that with infusion of 0.3 M NaCl ($P = 0.03$). These results of experiments with replacement of Na^+ by K^+ or Cl^- by Ac^- suggest that the absence of Cl^- is important for facilitating voluntary swallowing and that the presence of Na^+ does not affect initiation of swallowing. The results also suggest that K^+ has a weak stimulatory effect on mucosal receptors in the LP.

As shown in Figure 3A, facilitation of voluntary swallowing by water infusion tends to appear strongly in subjects with longer SI in the case of 0.3 M NaCl. To explore the respective role of sensory and cortical inputs in initiation of swallowing, SI with infusion of 0.3 M NaCl and SI with infusion of water shown in Figure 3A were analyzed. Figure 4A shows a comparison of SIs with infusion of 0.3 M NaCl and with infusion of water. Prolonged SI with infusion of 0.3 M NaCl varied greatly in the subjects, whereas shortened SI with infusion of water varied moderately in the subjects. Facilitation of swallowing by chemosensory inputs from water receptors was determined by subtracting SI with infusion of water from SI with infusion of 0.3 M NaCl in each subject. Even though application of solution induces mechanical and thermal effects, common mechanical and thermal effects would be cancelled by this

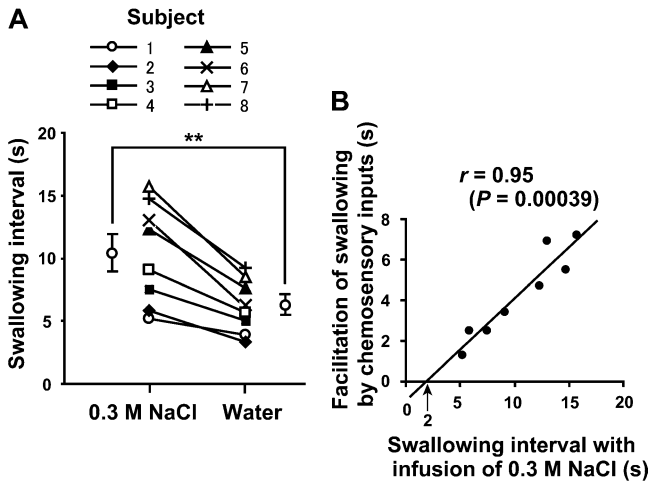

Figure 4 Comparison of SIs with 0.3 M NaCl and water for each subject. **(A)** Data from 0.3 M NaCl and water shown in Figure 3A are plotted again. Symbols represent 8 different subjects. Each subject number corresponds to the subject number shown in Figure 1B. SI was shorter in the case of infusion of water than in the case of infusion of 0.3 M NaCl in all subjects. Open circles and bar: means ± SEM $^{**}P < 0.01$, 0.3 M NaCl versus water. **(B)** Interaction between facilitation of swallowing by chemosensory inputs from water receptors and SI with infusion of 0.3 M NaCl. Facilitation of swallowing by chemosensory inputs from water receptors was defined by subtracting SI with infusion of water from SI with infusion of 0.3 M NaCl for each subject. The values of facilitation of swallowing by chemosensory inputs and SI with infusion of 0.3 M NaCl were obtained by data shown in (A). Statistically significant increase in facilitation of swallowing by chemosensory inputs is observed as a function of SI with infusion of 0.3 M NaCl ($y = 0.51x - 1.02$, $r = 0.95$, $P = 0.00039$). Extrapolation of the linear regression to the x axis (zero facilitatory effect) gives 2 s (see the arrow).

subtraction and only the effect of stimulation of water receptors with water would appear. To evaluate the role of chemosensory inputs from water receptors in voluntary swallowing, facilitation of swallowing by chemosensory inputs from water receptors is plotted against SI with infusion of 0.3 M NaCl (Figure 4B). There was a linear correlation between facilitation of swallowing by chemosensory inputs and SI with infusion of 0.3 M NaCl: the longer the SI with infusion of 0.3 M NaCl was, the stronger was the facilitation of swallowing by chemosensory inputs. A high correlation coefficient ($r = 0.95$, $P = 0.00039$) between them was obtained. Extrapolation of the linear regression to the x axis (zero facilitatory effect) gave 2 s. This value indicates the minimum SI in which facilitation of swallowing by chemosensory inputs does not appear.

Discussion

In our previous study (Yahagi et al. 2008), we investigated localization of water receptors and salt taste receptors in the PT and LP in humans. Our previous results suggested that water receptors are localized in the LP and that salt taste receptors are almost absent in the LP and are present in the PT. In the present study, solutions were infused exclusively into the LP. Therefore, the data obtained in this study provide information about characteristics of water receptors in the LP in humans.

Ionic properties of water receptors

In animal experiments, it has been shown that injection of isotonic saline to the LP was ineffective for eliciting swallowing reflex, but isotonic sucrose solution was almost as effective as water in initiating swallowing reflex (Storey 1968a, 1968b; Shingai and Shimada 1976). Therefore, the effect of water was not due to osmotic pressure. The mechanism of the excitation of water receptors has been studied by recording neural responses from single water fibers in the SLN in several animals. There are species differences in ionic properties of water receptors. In rabbits, Shingai (1977) showed that excitation of laryngeal water receptors is inhibited by small anions such as SCN^-, Br^-, Cl^-, I^-, and NO_3^- but not by large anions such as citrate, SO_4^{2-}, F^-, and acetate and that Na^+ is not important for inhibition of the activity of water receptors. Similar ionic specificities of water receptors in the SLN have been reported in puppies and adult dogs (Boggs and Bartlett 1982). From these findings, it has been proposed that excitation of water receptors is caused by absence or reduced concentration of Cl^- (or small anions such as SCN^-, Br^-, I^-, and NO_3^-). On the other hand, the activity of laryngeal water receptors in rats is inhibited by Na^+ but not by Cl^- (Shingai 1980). In general, water applied to the tongue does not produce a response of tongue chemoreceptors in most animals except cats (Bradley 2000). Inhibition of the response of lingual water receptors in cats by NaCl is due to Cl^- (Cohen et al. 1955), whereas data from cat laryngeal water receptors (Stedman et al. 1980) showed that Cl^- is not a critical factor for excitability of water receptors. Therefore, the mechanism of inhibition of the activity of water receptors can be divided into 2 types: Cl^--dependent type and Cl^--independent type. For humans, Shingai et al. (1989) reported characteristics of water receptors in the throat based on the results of an experiment on swallowing reflex. The properties of water receptors in humans, however, could be studied only at a low concentration (0.05 M) of salts. They showed that Na salts with large anions ($NaHCO_3$, NaAc, and potassium acetate) at 0.05 M were as effective as water for inducing swallowing reflex, whereas NaCl and KCl at 0.05 M prolonged the latency of swallowing reflex. Their findings revealed that Cl^- is a critical factor for suppressing initiation of swallowing reflex in humans. Hence, they proposed that water receptors in humans have almost the same ionic specificity as that of laryngeal water receptors in rabbits. In this study, we confirmed and extended their findings by showing ionic specificity of water receptors at a high concentration of salts with a method based on measures of SI in voluntary swallowing. In this study, NaAc at 0.3 M was as effective as water for facilitation of voluntary swallowing. NaCl and KCl at 0. 3 M prolonged

SI. These results clearly suggest that Na^+ and Ac^- do not affect the excitation of water receptors and that Cl^- is responsible for inhibition of the activity of water receptors by NaCl. Therefore, absence or reduced concentrations of Cl^- appears to be responsible for excitation of water receptors in humans. We found that SI was somewhat shorter in the case of infusion of 0.3 M KCl than in the case of infusion of 0.3 M NaCl (Figure 3). It appears that K^+ at relatively high concentrations has a weak stimulatory effect. A similar weak stimulatory effect of K^+ has been observed on responses of laryngeal water receptors in rabbits (Shingai 1977). Consequently, it appears that the mechanism of excitation of water receptors in the LP in humans is similar to that of laryngeal water receptors in rabbits and puppies. On the basis of results of single water fiber analysis in the SLN in rabbits, Shingai (1977) proposed that chloride channels that are permeable to small hydrated anions are involved in excitability of laryngeal water receptors. That is, removal of Cl^- in the mucus by application of water to the LP brings about an outflux of Cl^- via chloride channels that excites water receptors, whereas the presence of Cl^- in the mucus induced by application of NaCl solution bring about an influx of Cl^- that inhibits activity of water receptors. However, blockers of chloride channels have not been tested, and further details about the transduction mechanism are not known.

Laryngeal water receptors are chronically exposed to the fluids produced by the minor salivary glands. Ionic composition of the fluids secreted by the minor salivary glands is yet not known. However, Cl^- may be normally abundant in laryngopharyngeal fluid because short ducts of the minor salivary glands do not reabsorb Cl^- from the primary secretion derived from blood plasma. This suggests the existence of water receptors that are held in the normal resting state by the presence of Cl^- in its extracellular fluid. Laryngeal water receptors are excited when the salivary fluids bathing the mucosa in the LP are temporarily replaced with solutions of absence or reduced concentration of Cl^- (small anion).

Repeated voluntary swallowing with a dry mouth is difficult to maintain, and both inhibition of salivation by methyl scopolamine nitrate and surface anesthesia of the throat increase the difficulty in initiating swallowing in humans (Mansson and Sandberg 1975a, 1975b). These findings suggest that sensory stimulation of surface receptors with resting saliva (unstimulated saliva) produced by the major salivary glands (the parotid, submandibular, and sublingual glands) is important for initiation of swallowing. The ducts of the major salivary glands modify the primary secretion by extracting Na^+ and Cl^- from and adding K^+ and HCO_3^- to the saliva. Major anions of human submandibular saliva in the resting state contain very low concentrations of Cl^- (0.012 M) and HCO_3^- (0.0022 M) (Dawes 1974). The dose-SI curve for NaCl shown in Figure 2 indicated that infusion of 0.05 M NaCl gave rise to only a small prolongation of SI. HCO_3^- at 0.05 M applied to the throat was the same as water applied to the same region in humans (Shingai et al. 1989). Thus, it is likely that resting saliva (low concentration of Cl^-) produced by the major salivary glands can excite water receptors in the LP in humans. Because flow rate of resting submandibular saliva is very slow (0.26 mL/min) (Dawes 1974), it is possible that excitation of water receptors in the LP by a small amount of resting saliva precedes excitation of mechanoreceptors caused by a certain amount of resting saliva accumulated in the throat. Resting saliva decreases during sleep (Ferguson and Fort 1974) and spontaneous swallowing concomitantly decreases (Lear et al. 1965; Sato and Nakashima 2006). It appears that frequency of spontaneous swallowing is related to flow rate of resting saliva. This suggests that resting saliva secreted by the major salivary glands can excite water receptors and thereby cause spontaneous swallowing. Spontaneous swallowing occurs without conscious effort and plays an important role in clearance of the mouth of saliva. Therefore, excitation of water receptors by resting saliva may contribute to avoidance of aspiration.

Role of chemosensory inputs from laryngopharyngeal water receptors in voluntary swallowing

The increasing swallowing difficulties during repeated dry swallowing resulted from a lack of resting saliva secreted by the major salivary glands, due to withdrawals by previous swallowing (Mansson and Sandberg 1975a). In our previous study (Yahagi et al. 2008), we found that SI with infusion of 0.3 M NaCl at the infusion rate (0.2 mL/min) was very close to SI with dry swallowing without infusion of solutions. Thus, it is likely that infusion of 0.3 M NaCl into the LP at 0.2 mL/min serves as a nonstimulating solution.

With diminution of sensory inputs from the oral mucosa, cortical inputs would play a dominant role in voluntary swallowing. Infusion of the nonstimulating solution prolonged SI in voluntary swallowing. We found that there was high intraindividual reproducibility of SI and that there was considerable interindividual variation in SI with infusion of the nonstimulating solution (Figure 1B). This suggests that the ability of the central regulation of swallowing to initiate repetitive voluntary swallowing varies greatly in subjects. Facilitation of voluntary swallowing by chemosensory inputs from water receptors appeared strongly in subjects showing difficulty (longer SI with infusion of the nonstimulating solution) in voluntary swallowing (Figure 4). This finding may be explained as follows. The dorsal swallowing group neurons of the CPG receive convergent information from both cortical and peripheral inputs that trigger swallowing (Jean 2001). It is thought that cortical drive to the CPG varies greatly in subjects. Hence, it is suggested that facilitation of swallowing by chemosensory inputs appear strongly in subjects with longer SI caused by a weak cortical drive. On the other hand, facilitation of swallowing by chemosensory inputs did not appear in subjects with SI of 2 s (Figure 4B). In this case, the cortical drive is so strong that chemosensory inputs from water receptors cannot

contribute to shortening of the SI. We conclude that the chemosensory inputs compensate for the difficulty in initiating swallowing via the central neural mechanism. Recently, it has been shown that sensory inputs from mucosal receptors modulate swallowing cortical activity (Mistry et al. 2006; Teismann et al. 2007; Lowell et al. 2008). Therefore, sensory inputs from mucosal receptors might modulate both the cortical swallowing center and the bulbar swallowing center.

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