Current Topics

Taste and Health: Nutritional and Physiological Significance of Taste Substances in Daily Foods

Neural Mechanisms of Swallowing and Effects of Taste and Other Stimuli on Swallow Initiation

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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). Reflecting the progressive aging of society, patients with swallowing disorders (*i.e.*, dysphagia) are increasing. Therefore, there is expanding social demand for the development of better rehabilitation treatment of dysphagic patients. To date, many dysphagia diets have been developed and are available commercially to help bring back the pleasure of mealtimes to dysphagia patients. Texture modification of food to make the food bolus easier to swallow with less risk of aspiration is one of the important elements in dysphagia diets from the viewpoint of safety assurance. However, for the further development of dysphagia diets, new attempts based on new concepts are needed. One of the possible approaches is to develop dysphagia diets that facilitate swallow initiation. For this approach, an understanding of the mechanisms of swallow initiation and identification of factors that facilitate or suppress swallow initiation are important. In this review, we first summarize the neural mechanisms of swallowing and effects of taste and other inputs on swallow initiation based on data mainly obtained from experimental animals. Then we introduce a recently established technique for eliciting swallowing using electrical stimulation in humans and our ongoing studies using this technique.

Key words swallow; reflex; pharynx; taste; glutamate; human

1. INTRODUCTION

Reflecting the progressive aging of society, with from swallowing disorders (*i.e.*, dysphagia) are increasing in number. Oropharyngeal dysphagia is defined as "difficulty in initiating a swallow and/or moving the bolus from the oral cavity into the esophagus."[1,2] Although the aging process can produce measurable changes in the normal swallow, these changes alone are not sufficient to cause clinically apparent dysphagia. The causes of oropharyngeal dysphagia in the elderly are predominantly neuromyogenic, with the most common cause being stroke.[3,4]

People with dysphagia are at risk of developing serious complications 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) as well as feeding strategies to help formation of the food bolus and swallowing it.[3] Many dysphagia diets have been developed and are commercially available to help dysphagia patients bring back the pleasure to mealtimes. 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. An approach to reduce the risk of aspiration is very important from the viewpoint of safety assurance. However, for the further development of dysphagia diets, new attempts based on new concepts are needed.

One of the possible approaches is to develop dysphagia diets that facilitate swallow initiation. For this approach, an understanding of the mechanisms of swallow initiation and identification of factors that facilitate or suppress swallow initiation are important. For a decade, we have studied the neural mechanisms of swallow initiation and found possible facilitating or suppressing factors in experimental animals and humans. In this review, we first summarize the neural mechanisms of swallowing and effects of taste and other inputs on swallow initiation based on data mainly obtained from experimental animals. Then we introduce a recently established technique for eliciting swallowing using electrical stimulation in humans and our ongoing studies using this technique.

2. NEURAL MECHANISMS AND EFFECTIVE SENSORY INPUTS FOR 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 (pha-

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ryngeal stage or swallow reflex).[3,5—7] These events occur continuously (terminal swallow), but also occurs simultaneously (interposed swallow).[8] Although the oral stage of swallowing is under voluntary control, the swallow reflex is an innate semiautomatic reflex movement. It is now well established that the organization of the motor sequence 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).[9—11] Interneurons in the swallowing center organize the whole sequence of muscle contractions of swallowing, so that the control of swallowing is a property of a precisely interconnected set of neurons. The swallowing center can be anatomically and functionally divided into two neural networks, the dorsally situated interneurons including the nucleus of the solitary tract and the ventrally situated interneurons around the nucleus ambiguus in the medulla. The dorsally situated group of interneurons is responsible for initiating swallowing and programming the event of swallowing. The output of the dorsal group is distributed by the ventral group to the appropriate motor nuclei sending the motor command to each of the swallow-related muscles.[10—12]

The swallow reflex can be elicited from specific areas of the pharynx and larynx. Such areas are innervated by the glossopharyngeal nerve (GPN), the pharyngeal branch of the vagal nerve (Xph), and the superior laryngeal nerve (SLN). Effective stimuli eliciting the swallow reflex are mechanical, chemical, and thermal stimulation. In addition, in the laryngeal regions, water stimulation is effective in eliciting the swallow reflex.[13—15] In experimental animals, electrical stimulation of the peripheral nerves innervating the pharynx and larynx is also used to elicit the swallow reflex. In particular, repetitive electrical stimulation of the SLN can elicit the reflex "like magic."[11] On the other hand, it is much more difficult to elicit the swallow reflex by stimulation of the GPN than the SLN. This ineffectiveness of the GPN to initiate swallowing contradict the findings obtained by mechanical and other stimuli, since the GPN is a major peripheral nerve innervating the pharynx, from which the swallow reflex can be easily elicited by mechanical and other stimuli. By sectioning the pharyngeal branch of the GPN (GPN-ph) or lingual branch of the GPN (GPN-li) as well as selective electrical stimulation of these branches, we showed that the most effective areas for swallow initiation in the pharyngeal region are innervated by the GPN-ph, but not the GPN-li, and that the GPN-ph plays a major role in the initiation of the swallow reflex from the pharynx[12] (Fig. 1).

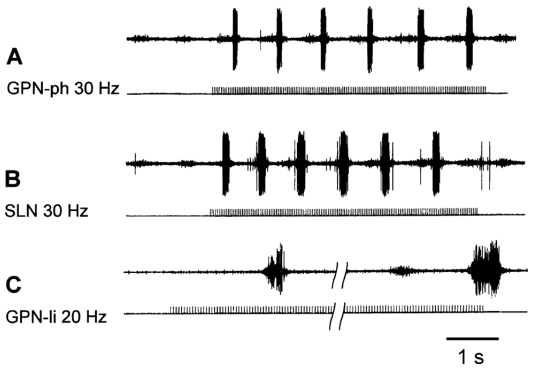

Fig. 1. Typical Examples of EMG Recordings from the Mylohyoid Muscle During Repetitive Electrical Stimulation of Peripheral Nerves

(A) and (B) Successive swallows elicited by electrical stimulation (0.5 V, 30 Hz, 1.0 ms) of the GPN-ph and SLN, respectively. (C) EMG activity during stimulation of the GPN-li (0.5 V, 20 Hz, 1.0 ms). Note that EMG bursts during GPN-li stimulation were different from those observed during swallowing. No swallow-related EMG activity was observed during GPN-li stimulation. Modified from Kitagawa *et al.* 2002.[14]

3. FACTORS MODULATING SWALLOW INITIATION

3.1. Inputs from the Higher Brain (Animal Study) Although it is generally believed that the whole sequence of the swallow reflex is mediated principally by the swallowing center,[16,17] considerable evidence suggests that the cerebral cortex may also play an important role in the initiation and regulation of swallowing.[18,19] Pathophysiologic evidence from stroke patients indicates that swallowing impairments are caused by cerebral cortex damage[20,21] and recent functional neuroimaging studies have shown changes in the activity of several cortical areas during swallowing in humans.[22—24]

Data from animal studies also indicate the possible involvement of the cerebral cortex in swallowing. Swallow-related neuronal activities were recorded in the face primary motor cortex in awake primates.[25,26] In addition, swallowing was evoked by stimulation of the pericentral cortex in primates,[27] or the frontal cortex in subprimates.[28,29] Furthermore, reversible inactivation of the lateral pericentral cortex in primates,[30] as well as ablation of the frontal cortex in rabbits,[31] caused swallowing impairments. We have also shown in rabbits that the cortical masticatory area (CMA), from which rhythmic jaw movements (RJMs) can be evoked by electrical stimulation and which plays an important role in the initiation and regulation of masticatory movement, has a modulatory effect on swallow initiation and the effect is site specific.[32] Namely, the posterolateral and deep part of the CMA that evokes RJMs with a prominent horizontal excursion of the jaw generally facilitated swallow initiation, and the anteromedial part and shallow CMA that evokes RJMs with small circular jaw movements did not affect swallow initiation (Fig. 2). The facilitatory effect of CMA stimulation on swallowing remained even after removal of peripheral sensory inputs by means of deafferentation of the infraorbital and inferior alveolar nerves innervating intraoral mechanoreceptors. The findings are consistent with the facts that the interposed swallow, which occurs during mastication, frequently occurs during the rhythmic chewing period when food is crushed between the molar teeth with a prominent horizontal excursion of the jaw, but rarely occurs during the preparatory period when food is transported to the back of the mouth with small circular jaw movements in the awake rabbits.[33]

3.2. Inputs from Orofacial Somatic Sensory Receptors (Animal Study) During natural feeding, various sensory inputs occur from the orofacial region such as movement-generated mechanical and proprioceptive sensory inputs from the periodontal receptors, the muscle spindles, the tongue and other mucosal receptors. Such sensory inputs also modulate swallow initiation, and the effect seems to be site specific. For example, Lowe and Sessle[34] reported a significant increase in the frequency of SLN-induced swallows when the maxillary cuspid was tapped during SLN stimulation, suggesting that swallow initiation is facilitated by periodontal sensory inputs. On the other hand, SLN-induced

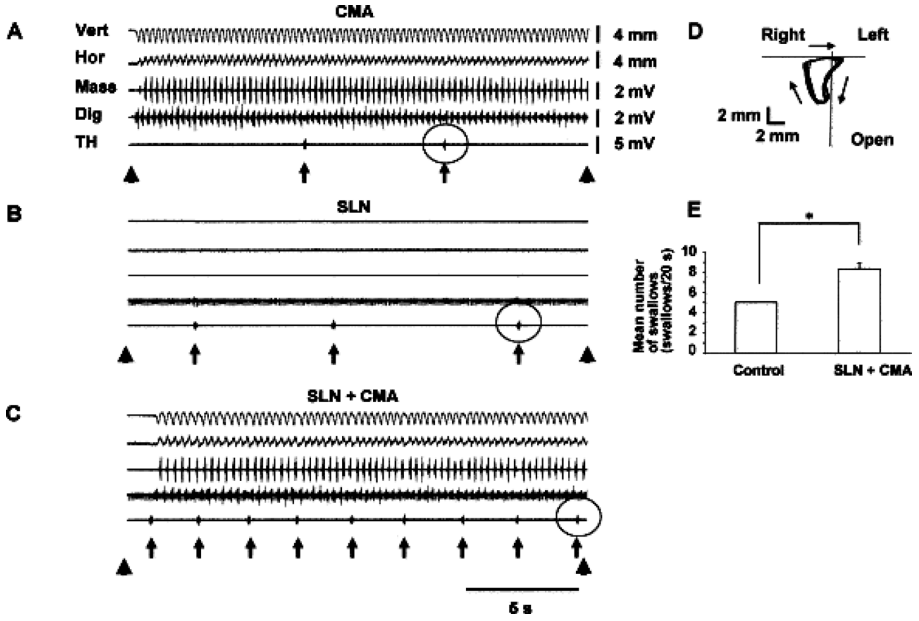

Fig. 2. Effects of Repetitive Electrical Stimulation of the Posterolateral and Deep Part of the CMA on Swallow Initiation (A)—(C)

For each of the three conditions ((A) stimulation of the CMA alone, (B) the SLN alone, (C) simultaneous stimulation of the SLN and CMA), the figure illustrates from top to the bottom the vertical (Vert) and horizontal (Hor) components of the jaw movement trajectories and EMG activities of the masseter (Mass), digastric (Dig), and thyrohyoid (TH) muscles. Both the CMA and SLN were stimulated at 0.6 mA (1.2 T eliciting rhythmic jaw movements and swallowing, respectively). The masseter and digastric EMG showed reciprocal activities and the pattern of RJMs was consistent throughout the RJMs (shown in (D)). Two swallows were evoked during CMA-alone stimulation, three swallows were evoked during stimulation of the SLN alone, and nine swallows were evoked during simultaneous stimulation of the SLN and CMA. The number of swallows evoked during simultaneous stimulation of the SLN and CMA (SLN+CMA) was significantly greater than the control (shown in (E)). * Significant difference between the values ($p<0.05$, paired t-test). Each arrow indicates a swallow. Arrowheads indicate the onset and offset of stimulation. Modified from Amarasena *et al.*[32]

swallows were reported to be inhibited during stimulation of the lingual branch of the GPN[14] and the lingual nerve,[35] suggesting that tongue sensory inputs have an inhibitory effect on the initiation of swallowing. In addition, Tsujimura *et al.*[36,37] have reported that the swallow reflex is inhibited by noxious stimulation to the orofacial region. In those studies, distilled water was infused through an infusion tube placed into the pharyngeal region to elicit the swallow reflex in anesthetized rats, and the number of swallows evoked was counted based on electromyographic (EMG) activity in the suprahyoid muscles. Then they showed that the number of swallows was decreased after the injection of capsaicin into the masseter muscle,[37] or the facial (whisker pad) skin or lingual muscle,[36] and the effect was dose dependent. They also suggested that neurons with γ-aminobutyric acid (GABA) receptors in the nucleus tractus solitarii plays major roles in this capsaicin-induced inhibition of the swallow reflex following noxious stimulation of facial and intraoral structures. The findings are consistent with clinical observations that inflammatory myopathy or severe oral pain after dental extraction is involved in swallowing abnormalities.[38,39] On the other hand, an other study showed that the number of swallow reflexes elicited in the same manner (*i.e.*, by injections of distilled water into the pharynx through a catheter) was decreased by the desensitization of NK1 receptors caused by capsaicin pretreatment in anesthetized guinea pigs, and suggested that the capsaicin-sensitive nonmyelinated C-fibers facilitate the swallow reflex.[40] The mismatch in the effect of capsaicin suggests that the effect of capsaicin on the swallow reflex is not uniform but site specific.

3.3. Inputs from Taste Receptors (Animal Study) In addition to sensory inputs from mechanical and other receptors related to somatic sensation, sensory inputs from special sense organs such as taste receptors are also reported to modulate swallow initiation. There is considerable evidence that sour taste facilitates swallow initiation.[41] We tested the effects of water, sour solutions, and other taste solutions applied to the mucosa of the pharyngolaryngeal region on swallow initiation in anesthetized rats, and showed that acetic and citric acids, which provide a sour taste, had a stronger facilitatory effect on swallow initiation as compared with other taste solutions[15] (Fig. 3). We also showed that such effects were caused by an increase in sensory inputs *via* the SLN and pharyngeal branch of the GPN. The finding is consistent with clinical observations that a sour taste bolus facilitates the onset of swallowing as compared with a nonsour bolus in patients with neurogenic dysphagia.[42]

3.4. Factors Modulating Swallow Initiation in Humans As noted above, electrical stimulation of the SLN and the GPN-ph can elicit swallowing in animals, and this technique was useful to study the possible modulatory effects of various inputs from the higher brain and sensory receptors on swallow initiation. However, only a few attempts have been made to elicit swallowing with electrical stimulation in humans,[43—45] and each of the methods has problems such as limited stimulation sites and difficulty in adjusting the electrode position. Therefore we tried to establish an effective way eliciting swallowing using electrical stimulation in humans.[46] Briefly, a custom-made monopolar silver electrode made with flexible metal tubing was introduced into the pharyngolaryngeal region via the nasal cavity under the endoscopic observation, and stimulated the posterior wall of the oropharynx or hypopharynx with repetitive electrical pulses. Swallows were identified by visual observation of movement of the larynx and EMG burst of suprahyoid muscles. Respiratory movements were monitored with a tension

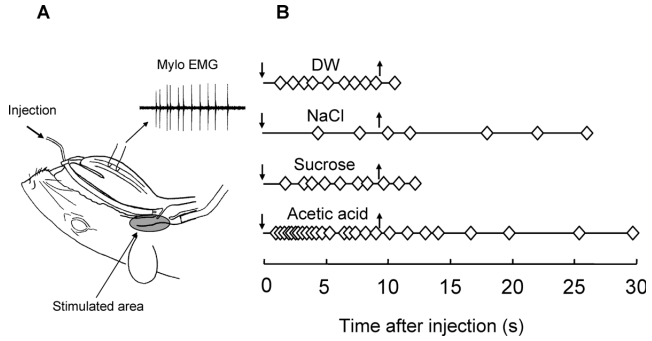

Fig. 3. Effects of the Application of Various Taste Solutions to the Mucosa of the Pharyngolaryngeal Region on Swallow Initiation

(A) Experimental diagram showing locations of an infusion tube inserted into a guide tube and a paired electrode for recording EMG activity from the mylohyoid muscle. An esophageal tube was fixed to drain solutions. An arrow indicates a typical example of EMG activity recording from mylohyoid muscle during swallowing. (B) Typical examples of successive swallows elicited by DW, NaCl (0.5 M), sucrose (0.5 M), and acetic acid (30 mM). The abscissa represents time from the onset of infusion. Downward and upward arrows indicate the onset and offset of infusion, respectively. Each open rhombus represents one swallow. Modified from Kajii *et al.*[15]

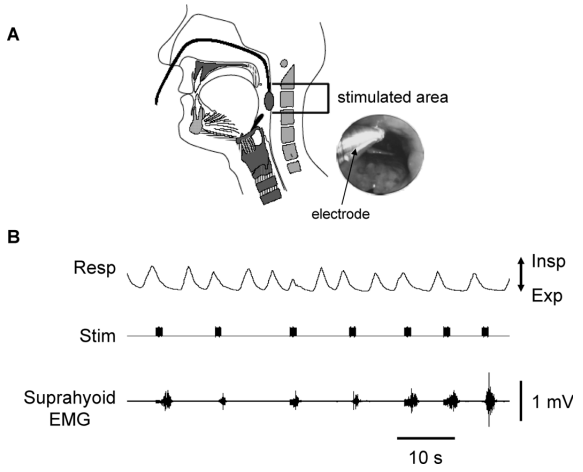

Fig. 4. (A) Diagrammatic Illustration of the System Eliciting Swallowing with Electrical Stimulation in Humans and Endoscopic Photography around the Stimulating Electrode and (B) Effects of Repetitive Electrical Stimulation (30 Randomly Applied Train Pulses, 1-ms Duration at 30 Hz, Maximum Intensity <0.8 mA) of the Posterior Wall of the Oropharynx

Swallows were consistently elicited by stimulation. The figure illustrates from top to the bottom the respiratory movements, stimulation pulses, and swallow-related EMG activities of the suprahyoid muscle.

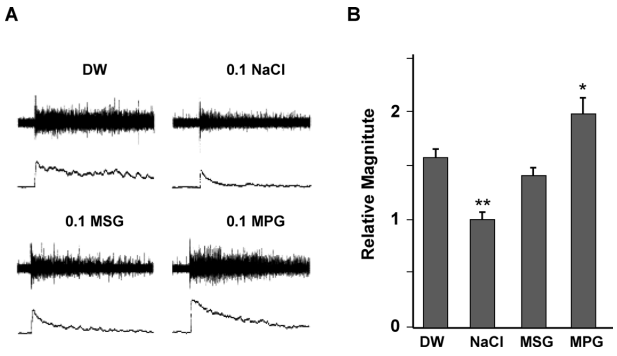

Fig. 5. Sample Spike and Integrated Recordings (A) and Relative Response Magnitudes Evoked from the GPN-ph of Rats ($n=8$) by Stimuli (DW, 0.1 M NaCl, 0.1 M MSG, 0.1 M MPG) (B)

Each of the magnitudes was calculated by the responses relative to the response to 0.15 M NaCl (physiologic saline), and results are shown as mean±S.E.M. The magnitude of integrated response for 0.1 MPG (2.01±0.13) was significantly higher than that of DW (*$p<0.05$, Dunnett's test). The magnitude of integrated response for 0.1 NaCl (0.98±0.07) was significantly less than that of DW (**$p<0.01$, Dunnett's test). Data suggest that the GPN-ph responds to MSG, but the sodium of MSG may inhibit the response of the umami substances. MPG, monopotassium glutamate. Modified from Kitagawa *et al.*[47]

sensor placed around the chest. Also, the subjects were asked to hold a switch and push it when stimulation was detected. We found that stimulation of both the oropharynx mainly innervated by the GPN-ph as well as the hypopharynx mainly innervated by the SLN successfully elicited swallowing (Fig. 4). The finding was consistent with our data obtained from animal experiments (see above).

We also found that the subjects reported that electrical stimulation of the oropharyngeal and/or hypopharyngeal region created the sensation of 1) flowing water, 2) water flow from a fountain, and 3) touch. This is consistent with the findings that many water receptors and mechanoreceptors exist in these regions. It was also notable that when the subjects tried to avoid swallowing, the suprathreshold stimulation (>1.5 T) did not elicit swallowing. This suggests that the swallowing reflex is heavily dependent on descending inputs from the higher brain.

Using this system, we started to identify factors that facilitate or suppress swallow initiation in humans. It is known that swallowing is episodic, with long swallow-free periods during sleep, although little is known about the influence of sleep in swallow initiation in response to peripheral stimulation. Therefore we tested whether the threshold of the swallowing reflex is increased during human sleep. The posterior wall of the oropharynx was stimulated by trains of electrical pulses (1-ms duration at 30 Hz, maximum intensity <0.8 mA) to elicit the swallow reflex, and swallows were identified by visual observation of movement of the larynx and EMG burst of suprahyoid muscles. Electroencephalograms were recorded to determine wakefulness and sleep. We found that the swallow reflex was consistently elicited during wakefulness but the incidence of such reflexively elicited swallows was decreased during sleep, suggesting that the threshold of the swallow reflex is increased during sleep.[46] The finding supports the view that enhancing wakefulness is important to evoke swallowing effectively and that it prevents aspiration as clinically suggested for dysphagia rehabilitation.

We are now testing the effects of taste stimulation of the pharynx on swallowing. For this, sensory inputs from the GPN-ph innervating the pharynx, playing an important role in the initiation of swallowing (as described above), have unique responses to taste stimulation which differ from responses of the chorda tympani nerve and lingual branch of the GPN. Electrophysiologic studies showed that water evokes a robust response. This is consistent with the finding that injection of water into the pharynx is an effective stimulus both in humans and animals. In addition to water, we found that the GPN-ph respond to solutions of umami taste [monosodium L-glutamate (MSG)] applied to the pharynx but not to NaCl solutions at physiologic concentrations in anesthetized mice and rats[47] (Fig. 5). Therefore we examined whether the application of MSG solution to the pharynx modulates swallow initiation. We have obtained preliminary data showing that the application of small amount of 0.1 M MSG solution to the pharynx increases the incidence of re-

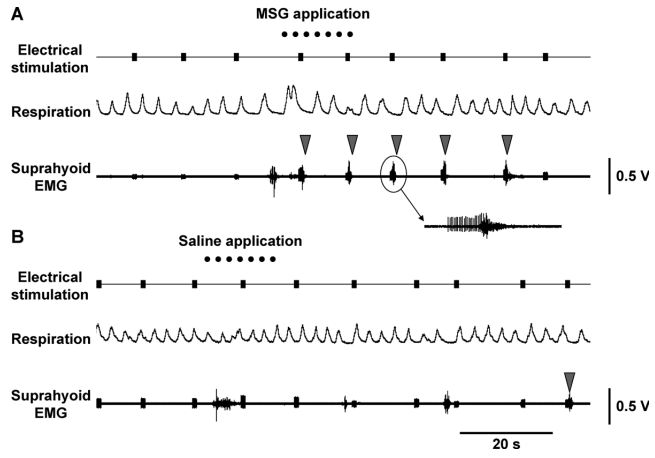

Fig. 6. Effects of 0.1 mM MSG Solution (A) and Saline (B) Application to the Posterior Wall of the Oropharynx on Swallow Initiation

Each solution of 50 μl was applied for 15 s. During each recording, peri-threshold electrical stimulation was applied to the posterior wall of the oropharynx to elicit the swallow reflex. The recordings from top to the bottom illustrate the timing of the application of each solution, electrical stimulation pulses to the oropharynx, respiratory movements, and swallow-related EMG activities of the suprahyoid muscle. Down-pointing triangles indicate the swallows elicited by electrical stimulation. The incidence of swallows elicited by electrical stimulation was increased after MSG application, but the effect was not observed after saline application.

flexively elicited swallows by electrical stimulation of pharynx at the threshold level (Fig. 6).

4. CONCLUSIONS AND PERSPECTIVE

We have shown that the initiation of swallowing can be modulated by various inputs from the peripheral nerves and the higher brain in experimental animals. The establishment of a system eliciting swallowing with electrical stimulation in humans enabled us to evaluate the modulatory effects of various factors on swallow initiation. This will help develop dysphagia diets that facilitate swallow initiation. Using the system, we found that the results on the initiation of swallowing obtained from experimental animals may also be applicable to humans. However, we also found that emotional and behavioral states sometimes overcome other modulatory effects on swallow initiation in the case of humans. Therefore, further study related to the modulatory effects of various behavioral states on swallow initiation will be needed.

We also believe that the establishment of the system will allow further progress not only in basic research but also in the diagnosis and rehabilitation of swallowing disorders. For example, eliciting swallowing using this system at the acute stage in poststroke patients may contribute to preventing disuse atrophy of swallow organs. It could also help conduct behavioral therapy with minimal risk of aspiration in patients with oropharyngeal dysphagia.

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