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Professor Special Lecture: 72nd Annual Meeting of the Medical Society of Toho University

Review Article

Pharyngeal Sensation and Dysphagia in Aspiration Pneumonia

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ABSTRACT: Although the etiology of aspiration pneumonia is multifactorial, there is a strong association between dysphagia and the development of aspiration pneumonia. However, it is still not clear why swallowing function decline with aging. Although recent research focused on dysphagia due to sarcopenia, which was defined as sarcopenic dysphagia, we should pay attention not only to the motor aspect, but also to the sensory aspect of dysphagia. Impaired pharyngeal sensitivity results in a delay of triggering swallowing reflex, which is a most serious problem in dysphagia. It is postulated that sensory receptors located in the pharyngeal mucosa or submucosa are similar to those in glabrous skin. In addition to the mechanoreceptors such as Merkel cell, Ruffini ending, and Meissner and Pacinian corpuscles, another sensory nerve subtype is thought to subserve pruriceptive pain and thermosensation in pharyngeal mucosa. In these free nerve endings, the transient receptor potential (TRP) channels were identified as cellular sensors of temperature and pain. We found that mechanorecptors and thermosensing TRP channels in the pharynx work synergistically to enhance the afferent signal to the swallowing center located at the brainstem. Aging deteriorates pharyngeal sensitivity by affecting sensory receptors, the peripheral nervous system, and microcirculation, resulting in altered detection, reduced sensory conduction, and abnormal efferent response. In addition, pharyngeal sensation is affected by central nervous system deficits. Heretofore, understanding of the molecular mechanism concerning the sense of touch in the pharynx was seriously limited. Mechanisms of touch sensation in the pharynx are, in some parts, similar to those of skin, but there must be differential mechanisms. In order to stratify the treatment of dysphagia, understanding the detailed mechanism of pharyngeal sensation is crucial. Future studies revealing the molecular mechanisms of pharyngeal sensation are warranted to prevent aspiration pneumonia.

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KEYWORDS: dysphagia, pharynx, aspiration pneumonia, temperature

Introduction

Pneumonia death is increasing rapidly due to increases of the aged population. Now, the pneumonia is 3rd leading cause of death in Japan, and most deaths for pneumonia occur in elderly people.[1] Most pneumonia cases in the elderly are aspiration pneumonia. With aging, the ratio of aspiration pneumonia to hospitalized pneumonia is dramatically increasing.[2] Aspiration pneumonia is induced by aspiration, which is defined as the misdirection of oro-

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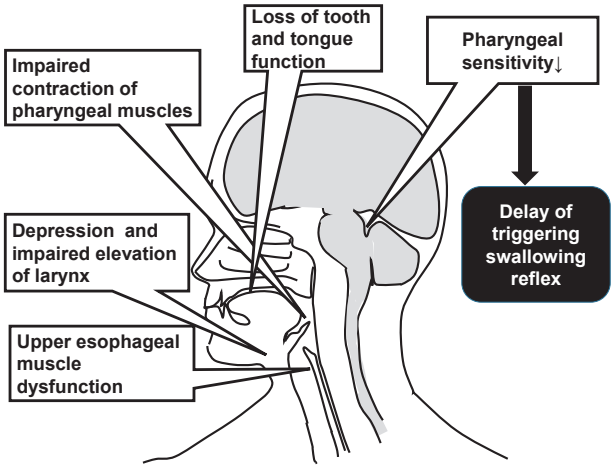

Fig. 1 The reasons for dysphagia associated with aging

pharyngeal or gastric contents into the larynx and lower respiratory tract. The recent, large scale, cross-sectional study in Japanese elderly people showed that the risk factors for aspiration pneumonia were sputum suctioning, dysphagia, dehydration, and dementia.[3] Although the etiology of aspiration pneumonia is multifactorial, there is a strong association between dysphagia and the development of aspiration pneumonia.[4] It has been suggested that the increased incidence of pneumonia with aging is a consequence of impairment of the swallowing reflex with senescence.[4]

Effect of Aging on Swallowing Functions

It is still not clear why swallowing function declines with aging. Roughly, dysphagia occurs due to loss of tooth and tongue function, impaired contraction of pharyngeal muscles, depression and impaired elevation of larynx, upper esophageal muscle dysfunction, and decreased pharyngeal sensitivity (Fig. 1).[5,6] The former three are based on dysfunction of muscles related to swallowing, and the last one is dysfunction of sensory component of swallowing. Recently, researchers focused on dysphagia due to sarcopenia, which was defined as sarcopenic dysphagia.[7]

However, we should pay attention not only to the motor aspect but also to the sensory aspect of dysphagia. Impaired pharyngeal sensitivity results in a delay of triggering the swallowing reflex, which is a most serious problem in dysphagia. Without timely induction of the swallowing reflex, food and oral secretions easily go to the airways. Although, in order to improve swallowing function, recovery of pharyngeal sensation is essential, the means of restoring it were seriously limited at the present stage because the mechanism how people percept food at pharynx has not been elucidated. Just recently, several studies concerning sensory receptors in the pharynx has been reported.[8–10]

Sensors of Pharyngeal Sensation

When food reaches the pharynx, the information of the arrival of the food was sent to the swallowing center at the brainstem. It is postulated that sensory receptors located in pharyngeal mucosa or submucosa are similar to those in glabrous skin.

In glabrous skin, innocuous touch is mediated by four types of mechanoreceptors, such as Merkel cell, Ruffini ending, and Meissner and Pacinian corpuscles.[11,12] The Merkel cell-neurite complex is in the basal layer of the epidermis. This mechanoreceptor consists of an arrangement between many Merkel cells and an enlarged nerve terminal from a single Aβ fiber. Merkel cells exhibit finger like processes contacting keratinocytes. The Ruffini ending is localized in the dermis. It is a thin, cigar-shaped encapsulated sensory ending connected to the Aβ fiber. The Meissner corpuscle, connected to Aβ nerve ending, is located in the dermal papillae. This encapsulated mechanoreceptor consists of packed down supportive cells arranged as horizontal lamellae surrounded by connective tissue. The Pacinian corpuscle is the deeper mechanoreceptor. One single Aβ unmyelinated nerve ending terminates in the center of this large ovoid corpuscle made of concentric lamellae.

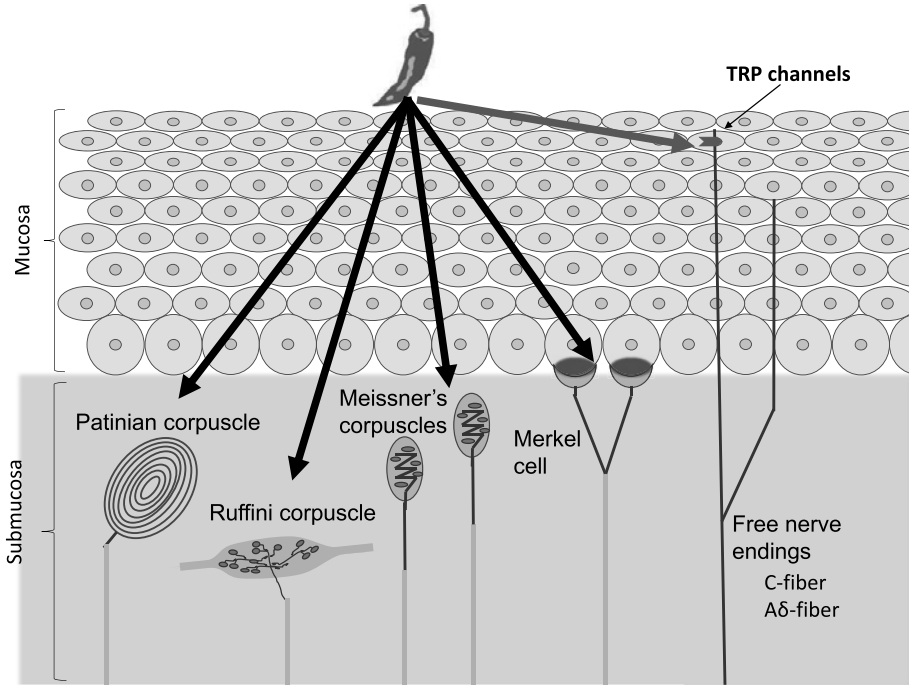

Fig. 2 Sensory receptors in pharynx and action sites of red chili pepper

In addition to the mechanoreceptors, another sensory nerve subtype is thought to subserve pruriceptive itch and thermosensation, which includes both unmyelinated C-fibers and thinly myelinated Aδ nerve fibers. In these free nerve endings, the transient receptor potential (TRP) channels were identified as cellular sensors of temperature, itch, and pain.[13–15] Just recently, using the biopsy sample of human pharynx, otolaryngologists found the organs resembling mechanoreceptors and free nerve endings represent TRP channels (Fig. 2).

Temperature and Swallowing Reflex

In order to understand pharyngeal sensation, it is important to know what kinds of sensory inputs can stimulate swallowing reflex in dysphagic people. We found that the swallowing reflex of elderly people is accelerated by temperature change. The latency of swallowing reflex was longest around body temperature (30-40℃) and the delay shortened with a difference in temperature apart from body temperature.[16] The results clearly showed that the swallowing reflex is stimulated by not only mechanoreceptors but also thermosensing TRP channels located on free nerve endings. Moreover, the results suggest that mechanorecptors and thermosensing TRP channels work synergistically to enhance afferent signal to swallowing center located at the brainstem (Fig. 2).

Our findings have many implications in practical care for elderly people. Since it is important to provide a variety of temperatures when serving meals, food should be prepared immediately prior to consumption. It is also important to stimulate the appetite and improve nutrition in elderly people who usually take time to eat.

Thermosensing TRP Channels and Its Agonists

The reception of outer temperature is carried out by peripheral sensory nerves that convert temperature stimuli into electric signals, which are then transmitted to the central nervous system. Mammals have six TRP channels on the peripheral sensory nerves, which are related to the reception of temperature: TRPV1, TRPV2, TRPV3, TRPV4, TRPM8 and TRPA1. Each has a different activation temperature threshold (TRPV1＞43℃, TRPV2＞52℃, TRPV3＞32-39℃, TRPV4＞27-35℃, TRPM8＜25-28℃ and TRPA1＜17℃).[17] Based on the relationship between water temperature and swallowing reflex sensitivity,[16] TRPV1, TRPV2, TRPM8, and TRPA1 may be related to activation of the swallowing reflex.

It has been shown that the swallowing reflex is temporally improved by acute stimulation of TRPV1 by capsaicin, a TRPV1 agonist.[18] As mentioned above, when food containing capsaicin, such as chili peppers, reaches the

pharynx, it stimulates both mechanoreceptor and TRPV1 channel simultaneously, resulting in sending the strong signal to the swallowing center. Based on the study, whether the swallowing reflex would be continuously improved by chronic stimulation of TRPV1 was examined using a troche containing capsaicin. When nursing residents were randomly divided into two groups and a capsaicin pastille or placebo was administered to each group for one month, the intervention group showed significant improvement in swallowing and cough reflexes.[19] This shows that chronic stimulation of TRPV1 in the mouth and pharyngeal region improved swallowing and cough reflexes. Therefore, the administration of a capsaicin pastille may prevent aspiration pneumonia in elderly people.

We also showed swallowing improvement by stimulation of the cold receptor TRPM8. Menthol, the main element of mint, was considered to provide a cool sensation. TRPM8, a cool/cold stimulation receptor gene was cloned as TRPM8, menthol receptor. Therefore, we infused a menthol solution of 10^{-4} M, 10^{-3} M, 10^{-2} M, or ice cold water into elderly people with delayed swallowing reflexes to measure the swallowing reflex. Delayed swallowing reflex shortened depending on the dose of menthol.[20] This suggests that drug therapy using menthol may show the same effects as physiotherapy, known as thermal stimulation,[21] which is currently used in rehabilitation of swallowing disorders.

Decline of Pharyngeal Sensitivity with Aging

With advancing age, a decline in the many sensory modalities, including touch sensation and perception, reportedly occurs.[22] Pharyngeal sensitivity to food also declines with aging. The pharyngeal sensation relies on the afferent function relaying the sensory information from the pharynx to the central nervous system, involving the mucous sensors and the transmission of the sensory stimuli to the higher brain structure. In the skin, it was reported that Merkel, Pacini and Meissner corpuscles decrease in number and have a structural deterioration with aging.[23] These morphological changes are very likely in the pharynx and must be correlated with declining pharyngeal sensitivity.

In addition to the morphological changes in the peripheral receptors, other abnormalities of the sensory systems, such as detection thresholds, nerve conduction velocities, structural changes of sensory fibers, and nerve fiber density, develop because of aging.[22] These influences are also considered to be involved in attenuation of sensation and sensitivity in the elderly. Moreover, the peptidergic afferent sensory nerves have an efferent function and stimulate target tissue by secreting neurotransmitters, which is known as the "axon reflex." The axon reflex may produce vasodilation of pharyngeal mucosa.[22] Although the vascular system is required to ensure efferent function of the afferent nerve fibers in the pharynx, aging can also affect the vascular system both morphologically and functionally.

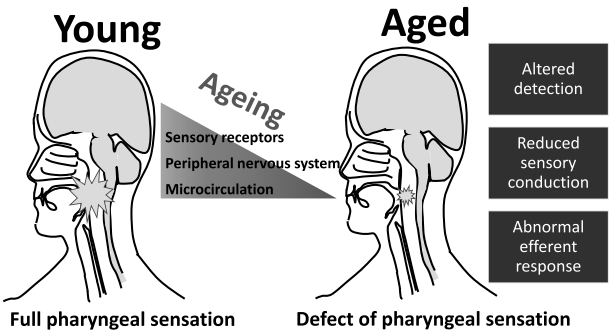

Fig. 3 Mechanism of decline in pharyngeal sensation by aging

Taken together, aging deteriorates pharyngeal sensitivity by affecting sensory receptors, the peripheral nervous system, and microcirculation, resulting in altered detection, reduced sensory conduction, and abnormal efferent response (Fig. 3). In addition, pharyngeal sensation is affected by deficit of central nervous system.

Improvement or Complement of Pharyngeal Sensation in Elderly People

In the way of advancement of geriatrics research, various methods to improve or complement pharyngeal sensation have been developed. In the first, using the thermosensing TRP channel agonists is a good method. The action of thermosensing TRP channel agonists, such as capsaicin and menthol, as anti-aspiration drugs were described at the previous sections.[18, 19] It is notable that the TRP channel thermoreceptor agonists have dual effects on the neural circuit of swallowing reflex. One is the direct (acute) effects on peripheral sensory neurons and the other is indirect (chronic) effects by repetitive thermal sensory stimuli to the insular cortex.

The smell of black pepper essential oil improved the swallowing reflex by activating the insular cortex and

promoting substance P-related neurotransmission.[24] Aromatherapy treatments, stimulated by this smell, are promising for a wide range of indications for dysphagia, and are feasible even in the elderly with low levels of ADL and/or very severe consciousness levels.

Cilostazol is a phosphodiesterase III inhibitor, which is commonly used for the treatment of cerebral infarction by increasing the cerebral blood flow and as an antiplatelet drug. Cilostazol is reported to increase the substance P and improve the swallowing reflex.[25] In addition, it can prevent aspiration pneumonia in the elderly by continuous administration.[26]

It is believed that activation of the dopaminergic system in the basal ganglia promotes neurotransmission involved in the swallowing reflex.[27] There is a report that the incidence of pneumonia was reduced by long-term administration of amantadine, a dopamine releaser.[28] Theophylline antagonizes adenosine A2 receptor at a concentration lower than that as a bronchodilator. Adenosine A2 is an inhibitory neurotransmitter, and adenosine A2 receptor is often present on the dopaminergic nerve. Therefore, theophylline causes disinhibition of dopaminergic neurons, activating the dopaminergic neurons at the basal ganglia, resulting in improvement of the swallowing reflex.[29]

Angiotensin-converting enzyme (ACE) inhibitors are agents that inhibit the angiotensin-converting enzyme. Since ACE breaks not only angiotensin I, but also substance P, an ACE inhibitor could increase serum substance P and improve swallowing reflex in patients with dysphagia. In a number of observational studies conducted among older Japanese and aging populations, the use of angiotensin-converting enzyme inhibitors, but not other blood pressure–lowering drugs, has been associated with a reduced risk of pneumonia.[30–37]

Conclusions

Heretofore, the molecular mechanism concerning the sense of touch in the skin has been well studied recently.[38, 39]

However, in the pharynx, the study about sensory mechanisms of pharyngeal sensation has just been started. Mechanisms of touch sensation in the pharynx are, in some parts, similar to those of skin, but there must be differential mechanisms from those of skin. In order to stratify the treatment of dysphagia, understanding the detailed mechanism of pharyngeal sensation is crucial. Future studies revealing the molecular mechanisms of pharyngeal sensation are warranted to prevent aspiration pneumonia.

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