

Review

Evaluation of the association between orofacial pain and dysphagia

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Abstract: Swallowing has a vital function in airway protection and is the next step after mastication. Swallowing impairment, which is known as dysphagia, is frequently accompanied by pain. Previous clinical studies have shown that orofacial pain affects swallowing function. Thus, it was hypothesized that orofacial noxious inputs may modulate swallowing function. Previous studies using anesthetized animals has proposed that the facial skin-nucleus tractus solitarius (NTS), masseter muscle-NTS, lingual muscle-NTS, and lingual muscle-paratrigeminal nucleus-NTS pathways may be involved in the inhibition of swallowing caused by facial, masseter, and lingual pain. Moreover, the activation of gamma-aminobutyric acidergic NTS neurons is involved in the inhibition of the swallowing reflex following trigeminal noxious inputs. This review focused on the recent management of dysphagia, neural mechanisms of swallowing, and relationship between orofacial pain and swallowing function. This and other future studies in this field can provide a better understanding of both normal and impaired swallowing and can help develop a new approach to treat patients with dysphagia and orofacial pain.

Keywords; dysphagia, pain, swallowing, trigeminal nerve

Introduction

In 2007, Japan became a super-aged society, which indicates that the proportion of individuals aged 65 years and older is more than 21% of the total population. In relation to this, the number of deaths caused by pneumonia has increased. The condition became the third leading cause of death in Japan in 2011, and approximately 96% of patients who died from pneumonia were aged 65 years or above [1]. Similar to this observation, Teramoto et al. have shown that the incidence of aspiration pneumonia increased with age [2]. This condition is caused by swallowing impairment, which is known as dysphagia [3,4]. Deterioration of swallowing function is considered a risk factor for aspiration pneumonia in the older population [5].

Swallowing is vital for airway protection and is one of the initial steps in food ingestion. In addition to aspiration pneumonia, dysphagia causes several problems, including asphyxiation, dehydration, and malnutrition. Kulkarni et al. have concluded that a high risk of asphyxiation in individuals with schizophrenia is attributed to drug-induced dysphagia and abnormal eating habits, such as fast eating, inappropriately large boluses, and inadequate chewing [6]. The occurrence of dehydration in older long-term care residents with dysphagia has been reported [7]. A prospective study has revealed that dysphagia may be a risk factor of malnutrition and lower respiratory tract infections in older individuals in the community [8]. This prospective study emphasized the importance of routine screening and treatment of dysphagia in the older population. Moreover, the effect of age on pain perception has been a topic of interest due to the demographic changes in life expectancy and high prevalence rates of clinical pain among older individuals. Several experimental studies have been conducted over the years, and cross-sectional studies have assessed age-related changes in pain perception, particularly pain thresholds and tolerance thresholds. For example, pain threshold increases with age, whereas tolerance threshold

decreases. This contrasting result may be attributed to the fact that older individuals have low tolerance to pain [9]. The current review focused on the recent management of dysphagia, neural mechanisms of swallowing, and relationship between orofacial pain and swallowing function. This and other future studies in this field can provide a better understanding of both normal and impaired swallowing and can help develop a new approach to treat patients with dysphagia.

Treatment of dysphagia

The pathophysiological nature of dysphagia can be explained by the following signs/symptoms: failure to propel the bolus properly and deficit in pharyngeal and/or laryngeal sensation. Furthermore, in the former, the causes of dysphagia are classified as functional, organic, and combined. Dysphagia therapy is required to prevent any related problems, including failure to propel the bolus, aspiration, or pharyngeal residue. Traditionally, there are two approaches used in dysphagia therapy, which are the compensatory approach and rehabilitative approach. The compensatory approach involves immediate enhancement of the safety and efficiency of swallowing to reduce any symptoms associated with dysphagia, and it includes posture adjustments and food modification. The rehabilitative approach involves long-lasting effects that improve swallowing function, and it includes swallowing-related muscle strength training. Momosaki et al. have reported that dysphagia rehabilitation with compensatory and rehabilitative approaches contributed to the return to total oral intake upon discharge in older patients with aspiration pneumonia who are hospitalized [10]. However, these approaches are difficult to apply to patients who cannot follow instructions.

Recently, a chemical approach used to treat dysphagia has received much attention. Researchers have shown that transient receptor potential (TRP) receptor agonists facilitate swallowing functions. TRPV1 is activated by a variety of sensations, including mechanical stress, pain, and heat, and capsaicin, a TRPV1 agonist [11]. Ebihara et al. have reported that daily capsaicin supplementation shortened the latency of the swallowing reflex in older people with a high risk of aspiration [12]. The authors have hypothesized that substance P, which is released from sensory nerves in the pharynx after capsaicin application, facilitates the initiation of swallowing [13]. Moreover, red wine polyphenols, which enhance TRPV1 activation, improve the swallowing reflex in older patients with dysphagia [14]. TRPV1 activation can significantly evoke the swallowing reflex even in anesthetized animals [15]. Menthol and cold water, which both activate TRPM8, shorten the latency of the swallowing reflex in older patients with dysphagia [16], and piperine, which is a dual TRPV1 and TRPA1 agonist, improved the safety of swallowing in patients with dysphagia [17]. Furthermore, Alvarez-Berdugo et al. have compared the effects of TRPV1, TRPA1, and TRPM8 agonists in patients with dysphagia, and results showed that TRPV1 stimulation had the strongest therapeutic effect on swallowing function [18]. Although carbonated liquids and citric acid can also improve swallowing function in patients with dysphagia, the associated mechanisms, including the target receptors, remain unclear [19-21].

Neural circuit for swallowing

A schematic diagram of the neural circuit involved in swallowing is shown in Fig. 1. The swallowing reflex is easily evoked by a variety of stimulations applied to the pharyngeal and laryngeal mucosa. Some ion channels, including TRPV1, TRPA1, and TRPM8, and the epithelial sodium channel are believed to be involved in the initiation of swallowing [16,17,22]. Information is conveyed via the glossopharyngeal and/or vagus nerves to the swallowing central pattern generator (CPG) in the medulla. Among the

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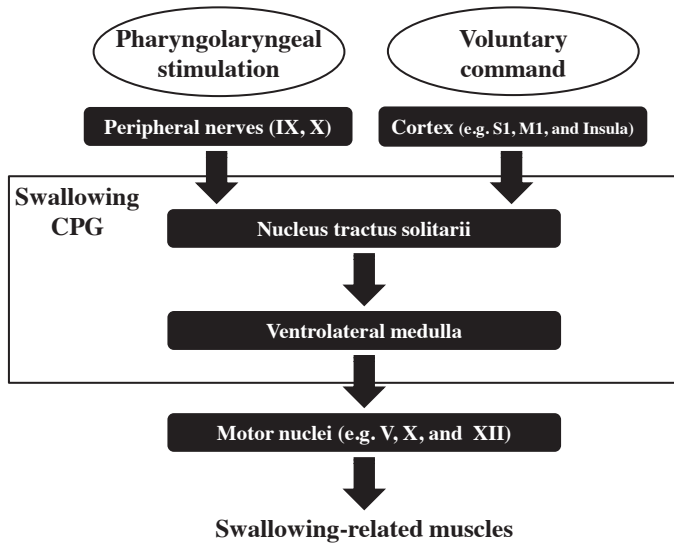


Fig. 1 Schematic diagram of the swallowing neural circuit. IX, glossopharyngeal nerve; X, vagus nerve; S1, primary sensorimotor cortex; M1, primary motor cortex; Insula, insular cortex; V, trigeminal motor nucleus; X, nucleus ambiguus and dorsal motor nucleus of the vagus; XII, hypoglossal motor nucleus; CPG, central pattern generator

branches of the glossopharyngeal and vagus nerves, the superior laryngeal nerve (SLN) may have a primary role in initiating the swallowing reflex [22]. The presence of a unilateral SLN lesion increased the incidence of aspiration in an infant animal model [23], and SLN afferents have important roles in facilitating laryngeal closure based on a human study [24].

Jean et al. have reported that interneurons in the swallowing CPG are mainly located in two areas: the nucleus tractus solitarii (NTS) and the ventrolateral medulla near the nucleus ambiguus [25]. Neurons in the former region are referred to as the dorsal swallowing group and are considered the generator neurons involved in the initiation of swallowing. Neurons in the latter region are referred to as the ventral swallowing group and are considered the switching neurons that drive motor neurons. Moreover, the *N*-methyl-D-aspartate (NMDA), non-NMDA, 5-hydroxytryptamine₁ (5-HT₁), and gamma-aminobutyric acid (GABA) receptors in the NTS can regulate the initiation of swallowing [26,27].

The swallowing CPG can be activated by not only peripheral inputs from the pharynx and larynx but also cortical inputs. Functional brain imaging studies have identified several cortical and subcortical regions that are activated by swallowing, which include the primary sensorimotor cortex, cingulate cortex, insular cortex, supplementary motor cortex, cuneus, precuneus, basal ganglia, thalamus, and cerebellum [28–31]. Clinical reports have emphasized the importance of the insular cortex in swallowing function. For example, Singh et al. have described a patient who presented with dysphagia after acute or subacute infarction involving the bilateral insular cortex [32]. In addition, Soros et al. have reported that electrical stimulation of the right insular cortex results in irregular and delayed swallowing in a patient with epilepsy [33]. Similar to these reports, it was previously revealed that electrical stimulation of the insular cortex evokes swallowing in anesthetized rats [34]. Moreover, cortically evoked swallowing was more strongly inhibited than peripherally evoked swallowing during rhythmic jaw movements evoked by electrical stimulation of the orofacial motor cortex [34]. This result indicates that peripherally and cortically evoked swallowing may be modulated differently by the masticatory system.

The swallowing CPG activates motor nuclei in the cranial nerves, including the trigeminal, facial, and hypoglossal nuclei; nucleus ambiguus; and dorsal motor nucleus of the vagus. Among these motor nuclei, the hypoglossal nucleus and nucleus ambiguus are the main motor nuclei correlated to swallowing motor activity [25]. Using nerve transection rat models, the hypoglossal nerve, arising from the hypoglossal nucleus, and the recurrent laryngeal nerve, arising from the nucleus ambiguus, were found to play a primary role in the generation of oropharyngeal and upper esophageal sphincter pressure, respectively, during swallowing [35].

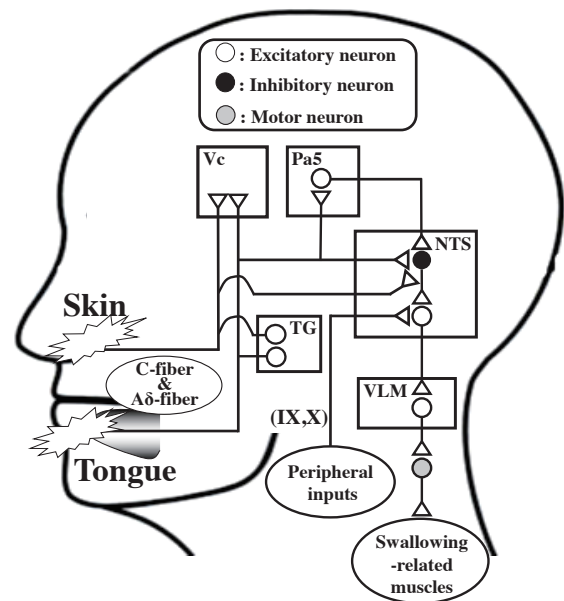


Fig. 2 Possible neural pathways of swallowing inhibition following orofacial noxious stimulation (adapted from Tsujimura et al. [62]). TG, trigeminal ganglion; NTS, nucleus tractus solitarii; Vc, trigeminal spinal subnucleus caudalis; Pa5, paratrigeminal nucleus; VLM, ventrolateral medulla; IX, glossopharyngeal nerve, and X: vagus nerve

Furthermore, Zoungana et al. have reported that the initial inhibition of motor neurons with a chloride-dependent hyperpolarization, followed by a depolarization in the nucleus ambiguus, during swallowing is important for the temporal organization of the swallowing motor sequence [36].

Orofacial pain and swallowing function

Dysphagia is frequently accompanied by pain [37,38]. Arijji et al. have reported that patients with odontogenic infections that had spread to the submandibular space experienced dysphagia and pain [39]. In addition, both dysphagia and non-cardiac chest pain are commonly observed in patients with gastroesophageal reflux disease [40,41]. In some cases, orofacial pain affects swallowing function. For example, patients with temporomandibular disorder (TMD), which involves frequent orofacial pain, present with symptoms of dysphagia. Gilheaney et al. have conducted a systematic review and meta-analysis of masticatory and swallowing function in adult patients with TMD [42]. The authors reported that 9.3% of patients had impaired swallowing and that 87.4% and 62% of patients complained of masticatory pain and masticatory fatigue, respectively. Fassicollo et al. have shown less activity in the suprahoid muscle during swallowing in chronic TMD patients with pain and abnormal displacement of the disc, thereby indicating that orofacial pain modulates the motor activity of swallowing [43]. Similar to this hypothesis, patients with myofascial pain dysfunction syndrome is prevalent hyperactive digastric muscles during swallowing [44]. Furthermore, increased duration of a single swallow, longer drinking time, and reduced masseter activity during swallowing have been reported in adult patients after the extraction of the lower second and third molars [45]. Clinical reports have hypothesized that orofacial noxious inputs modulate swallowing function. However, the precise mechanisms of disturbance and/or inhibition of swallowing have not yet been validated.

Modulation of swallowing function by trigeminal noxious stimulation

A previous literature has shown that noxious inputs can modulate jaw and orofacial motor reflexes. Wang et al. have investigated the effect of capsaicin-induced muscle pain on the amplitude of the jaw-stretch reflex in the masseter muscle, and results showed a stretch velocity-dependent increase in the amplitude of the jaw-stretch reflex during acute muscle pain in healthy participants [46]. In another study, the local application of mustard oil and excitatory amino acid receptor agonists to the temporomandibular joint region increased jaw muscle activity [47]. In addition, experimentally induced posterior temporalis muscle pain facilitated jaw-stretch reflexes and inhibited nociceptive-specific blink reflexes in healthy

participants [48]. The swallowing reflex is also affected by orofacial stimulation. Electrical stimulation of the lingual nerve inhibits the initiation of the swallowing reflex evoked by SLN electrical stimulation. Zoungana et al. have shown that this inhibition occurred at the level of interneurons around the NTS, which comprises the swallowing CPG as well as that of motor neurons and muscles [49], indicating that afferents from lingual nerves directly or indirectly inhibit the swallowing CPG. However, the previous studies had two methodological limitations. First, the type of nerve fibers activated by electrical stimulation is challenging to identify. Second, whether naturally evoked swallowing is modulated by the stimulation has not been fully elucidated.

Previous studies showed that capsaicin stimulation of the tongue, whisker pad skin, and masseter muscles, all of which are innervated by the trigeminal nerve, inhibited the initiation of swallowing by distilled water (DW) infusion into the pharynx [50,51]. These results strongly indicate that trigeminal noxious inputs inhibit naturally evoked swallowing by TRPV1 activation [11]. To validate the mechanism of inhibition of the swallowing reflex following trigeminal noxious stimulation, the activated areas in the brainstem were assessed after stimulation using phosphorylated extracellular signal-regulated kinase (pERK), which is considered a marker of excited nociceptive neurons [52]. Results showed that many pERK-positive neurons were expressed in the NTS and trigeminal spinal subnucleus caudalis (Vc) following the injection of capsaicin into the whisker pad, masseter muscle, and lingual muscles. Moreover, the injection of capsaicin into the lingual muscles induced pERK expression in the paratrigenial nucleus (Pa5). Similar to this result, previous immunohistochemical and electrophysiological studies have reported that these three nuclei are activated by trigeminal noxious stimulation [53–56]. Taken together with the previous reports which showed the direct projection from the trigeminal afferents to these three nuclei [57,58], this study showed that swallowing inhibition was diminished by intrathecal administration of the specific MAPK kinase (MEK) 1/2 inhibitor PD98059, indicating that ERK phosphorylation is involved in swallowing inhibition. Based on these results, the effects of NTS, Pa5, and Vc lesioning on swallowing initiation were evaluated. The number of DW-induced swallows was significantly lower after NTS lesioning with and without capsaicin stimulation compared with the sham operation. This result is consistent with previous findings showing that the NTS is the key component of swallowing initiation [25,59]. Furthermore, swallowing inhibition following capsaicin stimulation was diminished after Pa5 lesioning, but not Vc lesioning. Pa5 efferents project to the NTS [60]. Although the role of Pa5 in swallowing initiation under normal conditions remains unclear, it was suggested that the lingual muscle-Pa5-NTS pathway was involved in swallowing inhibition following noxious tongue stimulation. Furthermore, approximately half of the pERK-positive neurons in the NTS showed GABA immunoreactivity following capsaicin injection into the tongue and that microinjection of the GABA_A receptor antagonist bicuculline into the NTS diminished capsaicin-induced swallowing inhibition. GABA is the main inhibitory neurotransmitter in the central nervous system [61]. GABAergic neurons in the NTS are involved in the mechanisms of swallowing inhibition [26]. These findings indicate that the activation of GABAergic neurons in the NTS following trigeminal noxious stimulation may play an important role in swallowing inhibition. The possible swallowing inhibitory pathways are shown in Fig. 2. The facial skin-NTS, masseter muscle-NTS, lingual muscle-NTS, and lingual muscle-Pa5-NTS pathways might be involved in the inhibition of swallowing caused by facial, masseter, and lingual pain. It has also been speculated that the activation of GABAergic NTS neurons are involved in the inhibition of the swallowing reflex following trigeminal noxious inputs.

Discussion

To elucidate the neural mechanisms in patients with dysphagia after an orofacial pain, the effects of trigeminal noxious stimulation on the swallowing reflex must be investigated. Although previous studies have identified four possible pathways involved in the inhibition of the swallowing reflex, the following two questions remain: (1) what is the effect of noxious stimulations other than capsaicin, such as mechanical (pinch) and thermal (heat and cold) noxious stimulations, and (2) is cerebral cortex involved in capsaicin-induced swallowing inhibition? To answer the first

question, the effect of other types of stimulation, such as pinch, heat, and cold, on swallowing function should be evaluated using the same animal models. To answer the second question, a decerebration model must be used to evaluate the involvement of cortical activities after orofacial pain on swallowing function. Because of the complex and coordinated process, with five cranial nerves and more than 25 pairs of muscles, the peripheral and central swallowing mechanisms remain unclear. Swallowing studies using electrophysiological, neuropharmacological, immunohistochemical, and behavioural techniques must be conducted to validate the mechanisms of swallowing. A basic clinical collaboration is important to better understand the relationship between orofacial pain and dysphagia.

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Conflict of interest

None.

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