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TOPIC HIGHLIGHT

The Effects of Sensory Stimulation on Neurogenic Oropharyngeal Dysphagia

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ABSTRACT

Sensory input is crucial for the initiation and modulation of the swallow response. Patients with neurogenic oropharyngeal dysphagia present severe impairments in oropharyngeal sensitivity associated with impaired motor responses. Several strategies have been used with the aim to modulate the swallow response by modifying the sensorial properties of the bolus (either chemically or physically) or by directly stimulating the sensory and motor neurons of the pharynx and larynx. Most of the stimuli described as swallow sensory stimulants (such as acid, capsaicin or piperine) are integrated by receptors of the multimodal transient receptor potential (TRP) channel family, mostly expressed in sensory nerves. Enhancing the sensorial stimuli may increase the sensorial input to the swallowing centre of the brain stem, thus triggering the swallow response earlier and protecting the respiratory airway. Moreover, sensorial stimuli may promote brain plasticity, facilitating the recovery of deglutition. The aim of this review is to briefly summarize the effects of swallow therapies focused on sensory stimulation and discuss their effects, rationality, action mechanism and perspectives in patients with neurogenic oropharyngeal dysphagia.

Key words: Deglutition; Deglutition disorders; Therapy; Sensation; Taste

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INTRODUCTION

Treatments for oropharyngeal dysphagia (OD) have tended to focus on compensating the swallow dysfunction through the adoption of different postures and manoeuvres during swallowing and the modification of the bolus consistency. These treatments are widely accepted in clinical practice but evidence supporting their effectiveness in OD associated to aging or neurological diseases is limited, and patients and caregivers often have difficulties learning, teaching, managing and performing these strategies properly[1,2,3]. Diet modification such as the increase of fluids viscosity, has been more successful in reducing aspirations and penetrations[4] and in preventing aspiration pneumonia[5]. However, thickeners do not improve the physiology of the swallow response, and they may modify the palatability of some beverages[6] leading to poor compliance by patients.

In addition, behavioural strategies focused on exercise and swallow rehabilitation have been developed. These exercises aim to increase muscle strength and improve the motion of oropharyngeal structures, as well as favour central neuroplastic modifications[1,7].

Finally, several authors tried to treat oropharyngeal dysphagia by increasing sensorial input in a variety of ways, such as chemically, physically or electrically. It is generally assumed that, under normal function, the swallowing centre receives strong afferent input suggesting the involvement of sensory feedback during swallowing, and that sensory input is crucial to the initiation and modulation of the swallow response. Sensorial deficits of the pharynx and larynx after stroke[8] or in the elderly[9] are very prevalent and associated with the presence of aspirations. The disruption of the sensory feedback in healthy volunteers by the application of topical anaesthesia in the oropharyngeal mucosa reduces the cortical

control of swallowing, leading to tracheobronquial aspiration[10,11]. The aim of this review is to summarize the effects of sensory stimulation on the swallow function of patients with dysphagia and discuss their rationality, action mechanisms and clinical perspectives.

METHODS

A literature search was performed on the PubMed electronic database. The search was limited to publications in English up to September 2013 and the terms deglutition disorders or oropharyngeal dysphagia or swallowing combined with sensory stimulation or sensory stimulus were used. A total of 200 articles were found. A manual search of cross-references was also performed. Studies done on healthy volunteers and animals were used to discuss the action mechanism and rationality of these therapies. Articles discussing oesophageal disorders, anatomic disorders or paediatric pathologies were excluded.

SENSORY STRATEGIES TESTED IN DYSPHAGIC PATIENTS

Several strategies have been tested as modulators of the swallow response, modifying the sensorial proprieties of the bolus (either chemically or physically) or directly stimulating the sensory and motor neurons of the pharynx and larynx.

Chemical stimuli

Acid: Sour boluses (50% lemon juice) were one of the first strategies used to stimulate the swallow response in stroke and other neurological patients. Both groups of patients showed significantly improved onset of the oral swallow in response to sour boluses compared to non-sour boluses; stroke patients also exhibited reduced pharyngeal delay time, oral transit time and improved swallow efficiency, whereas the other neurological patients exhibited reduced aspiration[12]. Pelletier and Lawless[13] tested different concentrations of citric acid (2.7% and 1.11% w/v) and sucrose (8%) mixture in patients with neurological disorders and concluded that the highest concentration of citric acid (2.7%) significantly improved swallowing by reducing the rate of aspiration and penetration whereas sweet–sour mixture did not significantly improve swallowing behaviours. The combination of cold and sour taste produces distinct changes in swallowing physiology: reduced volume per second and smaller capacity (volume taken) per swallow[14], reduced oral transit time[15] and reduced pharyngeal transit time in ischemic hemispheric stroke patients[16,17].

Pungency: Pungent ingredients, such as capsaicin (Capsicum sp) or piperine (Piper nigrum), have also been tested in dysphagic patients to evaluate their therapeutic effect. Acute administration of capsaicin (10^{-8}-10^{-6} M) reduced the latency of swallow reflex (time from 1 mL of distilled water instillation into the pharynx to the onset of swallowing)[18]. Moreover, daily administration (10^{-6} M) also shortened the latency of swallow in elderly patients with dysphagia, particularly in older people at high risk of aspiration[19]. In a group of patients with dysphagia associated with aging, neurodegenerative diseases or stroke, capsaicin boluses (1.5×10^{-4} M) reduced the prevalence of penetrations into the laryngeal vestibule by shortening the laryngeal vestibule closure time and improving the hyoid movement[20]. Capsaicin boluses also reduced the prevalence of oropharyngeal residue by increasing the propulsion force[20]. In addition, 30 days of olfactory stimulation using black pepper oil also shortened the latency of swallow in a group of post-stroke dysphagic patients[21]. The supplementation of the alimentary bolus with piperine (1.5×10^{-4} M and 1×10^{-3} M) also reduced the prevalence of penetrations by shortening the laryngeal vestibule closure time[22].

Menthol: menthol boluses (10^{-4} M-10^{-2} M) given to 14 institutionalized elderly patients with dysphagia had a concentration-dependent effect on triggering the swallowing reflex (shortening the latency time)[23].

Carbonation: The use of carbonated liquids (citric acid/ sodium bicarbonate) has also been tested as a treatment strategy for dysphagic patients. It has been reported that carbonated thin liquids reduced prevalence of penetrations and aspirations, pharyngeal transit time and pharyngeal retention when compared with still liquids[24,25].

Mechanical stimuli

Tactile-thermal stimulation of the anterior faucial pillars is a traditional method to treat patients with neurogenic dysphagia, but evidence is scarce. Pommerenke[26] studied tactile stimuli at several places in the oral cavity and found that the faucial pillars were the most sensitive in triggering swallowing. Kaatzke-McDonald *et al*[27] showed that the combination of tactile with cold stimuli induced swallowing more efficiently, suggesting the existence of thermal receptors in the faucial pillars. Lazzara *et al* observed that stimulation improved triggering of the swallowing reflex in 23 out of 25 neurologically-impaired patients after a single-session treatment. However, Rosenbek found inconsistent results in his studies with dysphagic stroke patients[28,29,30] after 2 weeks of tactile-thermal application. Regan *et al*[31] reported significant improvement of swallowing motor function in patients with Parkinson's disease, showing that tactile-thermal stimulation of faucial pillars reduced the pharyngeal transit time, total transit time and pharyngeal delay time compared with no stimulation. Mechanical stimulation of the faucial pillars alone, without thermal stimuli, did not show significant changes in swallowing parameters in healthy volunteers[32,27]. Air-pulses have also been used to mechanically stimulate the oropharynx in individuals with dysphagia after a hemispheric stroke in a pilot study, showing increased resting swallowing rates in some individuals after bilateral application[33].

Thermal stimuli

Temperature changes combined with other sensory stimuli (such as acid or touch) have been described as a therapeutic strategy for dysphagic patients. Changing bolus temperature alone has also been tested in dysphagic patients, showing that temperatures above (60-80 ℃) and below (10-20℃) body temperature, accelerated the onset of swallow response in elderly patients with aspiration pneumonia[34].

Electrical stimuli

Intrapharyngeal electrical stimulation: the application of electrical stimuli on the pharynx of acute post-stroke dysphagic patients, using intra-pharyngeal electrodes (5 Hz, 10 min), showed a significant reduction in the pharyngeal transit time, swallowing response time and prevalence of aspirations[35]. These effects were associated with a marked increase in pharyngeal corticobulbar excitability and topographic representation in the undamaged hemisphere. A 3-day treatment (10 min/day, 5 Hz) improved airway protection compared with controls, reduced aspirations, improved feeding status and resulted in a shorter time to hospital discharge 2 weeks after the intervention[36].

Transcutaneous electrical stimulation: Transcutaneous electrical stimulation is used to activate muscles involved in swallowing

function through stimulation of peripheral motor nerves (neuromuscular electrical stimulation, NMES)[37]. However, their effectiveness and safety in the treatment of dysphagia is still under discussion[38,39] and studies evaluating NMES therapy present inconsistent results[40,41,42,43]. Transcutaneous electrical stimulation has also been used as a sensory strategy, avoiding muscle contraction during the treatment[44,42]. This stimulation strategy has shown significant improvement in several swallow parameters, such as reduced swallow response time and prevalence of aspirations in chronic post-stroke dysphagic patients[44,42] but not in dysphagic patients with Parkinson's disease[43].

PERIPHERAL TARGETS FOR SENSORY STIMULATION

Up to three sensory systems, olfaction, taste, and somatosensation, are involved in the detection of chemicals in food. Signalling of taste involves the activation of receptors located in the taste buds. Salts and acids utilize apically located ion channels for transduction, while bitter, sweet and umami (glutamate) stimuli utilize G-protein coupled receptors and second messenger signalling mechanisms. The receptor cells for smell are modified sensory neurons located in the upper part of the nasal passages. In addition, some chemical agents can activate ionotropic receptors of the trigeminal, glossopharyngeal and vagal nerves, leading to changes in ionic permeability and depolarization of sensory neurons. The ability of chemical substances to evoke sensory responses is known as chemesthesis. These fibres, specifically the maxillary branch of trigeminal nerve, pharyngeal branch of the glossopharyngeal nerve (GPNph) and two branches of the vagus nerve, the pharyngeal branch (Xph) and the superior laryngeal nerve (SLN), innervate the most sensitive areas to trigger the oropharyngeal swallow response, such as the palatopharyngeal arch, the edge of the soft palate in the pharyngeal region, the edge of the epiglottis and the aryepiglottic fold[45].

These afferents project to supra-medullar structures and to the swallowing centre in the brainstem and express several receptors of the multimodal transient receptor potential (TRP) channels, which integrate most of the stimuli described as swallow sensory stimulants:

Chemical stimuli

Acid: Acidic solutions activate and sensitize the trigeminal, the GPN and the SLN. Studies in rats showed that facilitation of swallowing by sour bolus (5 mM-30 mM of acetic acid or citric acid) may be due to increases in sensory inputs via the SLN and GPNph[46]. The stimulatory effect of H^+ on sensory neurons is essentially mediated by Transient Receptor Potential Vanilloid 1 (TRPV1) and Acid-Sensing Ion Channels (ASICs). TRPV1 have six transmembrane segments (TM) which form a pore permeable to Ca^{2+}. pH< 6 leads to the pore aperture as H^+ ions act in the extracellular domain, particularly in the Glu-648, Val- 538 and Thr-633, while for pH 6-7, H^+ act in the Glu-600, which does not cause the opening of the channel, but facilitates it to agonists such as capsaicin and heat[47,48]. In addition, ASICs expressed in sensory neurons respond to minor acidosis and lead to fast and rapidly inactivating inward Na^+ currents[49].

Pungency: It is well known that pungent compounds such as capsaicin and piperine exert their action mainly through TRPV1[50], although piperine can also activate the transient receptor potential anakrin 1 (TRPA1)[51]. TRPV1 expression has been found in nerve fibres in the subepithelial tissue of the human and rat epiglottis[52,53,54], in fibres surrounding the taste papillae in the anterior tongue[55] and in the trigeminal nerve[56].

TRPV1 stimulation by these agonists might therefore increase the sensory input to the brainstem and cortical areas, facilitating deglutition, as will be discussed later. In addition, the release of substance P (SP) and other neuropeptides by the sensory afferents on the oropharynx and larynx may exert a local effect. SP widely co-localizes with TRPV1 on C and Aδ fibre terminals and is released by the action of the TRPV1 agonists. Tachykinins like SP phosphorylate TRPV1 via PKC and sensitize the receptor[57]. Thus, either through direct action of SP and other neuropeptides on sensory nerve terminals or through the action of pro-inflammatory substances released due to the action of these neuropeptides, the release of SP into the larynx can produce sensitization of primary sensory neurons which facilitates the motor swallow response. SP may also play a major role in the cough reflex, another important protective reflex of the airways. One-month intervention using black pepper oil olfactory stimulation, increased serum SP levels compared with the period before the treatment[22]. In contrast, 7-fold lower SP concentrations were found in older patients with aspiration pneumonia (21.2±2.4 fmol/mL) compared to elderly controls (142.2±8.4 fmol/mL, $p<0.001$)[58].

Menthol: Menthol is a transient receptor potential melastatin 8 (TRPM8) agonist[59,60]. TRPM8 is a cold-sensing TRP channel expressed in several populations of sensory nerves such as trigeminal ganglions and nerve fibres in the tongue[61]. Although TRPM8's expression on the human pharynx and larynx is still unknown, its activation can also facilitate the swallow response, increasing the sensory input to the brain stem swallowing centre.

Carbonation: The carbon dioxide dissolved in water in carbonated liquids diffuses into cells and produces intracellular acidification, which could gate TRPA1 channels[62]. In the periphery, TRPA1 is expressed in a subset of nerve fibres in the human pharyngeal epithelium[63]. The stimulation of TRPA1 by carbonated beverages may be responsible for the increase in sensory input to the brainstem and supramedular areas, facilitating deglutition. Moreover, activation of mechanoreceptors by the CO_2 bubbles, a mechanical mechanism, can also be involved in the chemestesis induced by CO_2.

Mechanical stimuli

Alteration in peripheral receptor characteristics and changes in the swallow centre following the application of a stimulus have been proposed as possible neurophysiological mechanisms responsible for the improvements in swallow response observed after tactile-thermal stimulation[32]. Several receptors (either ionotropic or metabotropic) might be activated by a mechanical stimulus, leading to changes in ion permeability of the sensory afferents which can elicit an action potential. It has been reported that TRPA1 contributes to the mechanosensory function in visceral afferent endings[64]. Although its involvement in the response to tactile stimulation has not been explored, it might be responsible for the conduction, at least in part, of this therapeutic strategy which is normally applied together with cold stimuli, also conducted through the TRPA1. However, the application of mechanical stimuli alone does not seem enough to produce any significant change in swallow function[32,27], at least in healthy volunteers.

Thermal stimuli

Several members of the TRP family have been described as thermo-channels and are expressed in primary sensory nerve terminals where they provide information about thermal changes in the environment. TRPV1-4 are activated by elevated temperatures ranging from warm (TRPV3 and TRPV4) to more extreme heat (TRPV1 and TRPV2),

whereas TRPM8 and TRPA1 are activated respectively by moderate to noxious cold[65]. Therefore, the application of a thermal stimulus to the oropharynx can be integrated by these receptors, increasing the sensory input to the brainstem and cortical areas.

Electrical stimuli

Several animal studies and clinical studies in humans have shown that the application of an electrical stimulus to the SLN elicits swallowing. The electrical stimulation of GPNph plays the major role in the initiation of swallowing from the pharynx, GPNli electrical stimulation inhibits swallowing and Xph is not associated with the initiation of swallowing[45]. Dependent-voltage channels of these sensory neurons might be activated by means of sensory electrical stimulation (either intrapharyngeal or transcutaneous), and the input signal conducted to superior areas.

CENTRAL ACTION MECHANISM OF SENSORY STIMULATION

Even though the pharyngeal phase of swallowing has been often described as a reflex response, several studies show that it can be modulated by cortical and sensory inputs. The magnification of the sensorial stimuli may increase the sensorial input to the swallowing centre of the brain stem, leading to earlier threshold achievement in initiating deglutition thus protecting the respiratory system. Moreover, sensorial stimuli may reorganize the motor cortex, facilitating deglutition.

Brainstem

The brainstem swallowing centre, also referred as central pattern generator, is located in the medulla oblongata. This swallowing centre is formed by two groups of interneurons: the dorsal swallowing group (DSG), located in the spinal cord within the nucleus tractus solitaire (NTS), and ventral swallowing group (VSG), located in the ventrolateral medulla just above the nucleus ambiguus. The synaptic response of the interneurons of the DSG occur with a very short, stable latency of 1 to 2 ms, indicating that at least some of these neurons are monosynaptically connected to afferent fibres in the oropharynx. With regard to VSG neurons, several pulses are generally required to initiate the synaptic spike, the latency of which is visibly longer (7-12 ms) and variable, suggesting the existence of a polysynaptic pathway. Interestingly, a synaptic response can also be initiated in oropharyngeal neurons by stimulating a specific cortical area which induces swallowing, with a latency shorter in the DSG (5-8 ms) than in the VSG neurons (10-16 ms). These results suggest that the neurons of the VSG are probably activated via neurons of the DSG, and that the DSG interneurons are responsible for generating the pattern of swallow response when achieved the threshold to initiate deglutition, while VSG neurons are responsible for distributing the response to the different motor nuclei. The DSG neurons receive convergent information from both cortical and peripheral inputs to trigger the swallow response[66]. It should be noted that simultaneous stimulation of SLN and GPNph, decreased the latency of swallowing more than stimulating each nerve independently, suggesting that the combination of spatiotemporal primary sensory signals might also enhance and strengthen the swallow response[67]. Changes in the pattern or frequency of peripheral sensory input might lead to changes in the NTS neurons, such as the excitability of neurons and the traffic and release of neurochemicals, which could contribute to modifying the swallow response[68]. Most synapses, including those in the NTS, are subject to changes in synaptic efficacy and output due to the influence of the presynaptic input. Although neuroplasticity phenomena in the NTS related to swallowing stimulants have not been studied specifically, the NTS possesses a remarkable degree of plasticity in response to a variety of stimuli, both acute and chronic[69], that could be involved in the changes in the swallowing behaviour observed after sensory stimulation.

Supramedular areas

Although swallowing control is mainly mediated by brain stem mechanisms, the cerebral cortex also plays a fundamental role in the initiation and regulation of the swallow response. Several clinical reports from stroke patients have indicated that cortical damage causes swallowing dysfunction[70]. Moreover, changes in the activity of several cortical areas during swallowing have been reported by means of neuroimaging studies and the effect of sensory stimulation of the oropharynx on cortical function and excitability has been investigated by several authors. It has been reported that sour boluses increase cortical activation in the swallowing neural network (sensory-motor cortex, insula, cingulated gyrus, prefrontal cortex, precuneus, supplementary motor area) compared to saliva and water swallows[71,72]. Ebihara *et al*[21] found that 30 days of olfactory stimulation with black pepper increased the cerebral blood flow in the right orbitofrontal and left insular cortex in older people with swallowing dysfunction and resulted in improved swallowing. Carbonated solutions have been shown to increase cortical excitability of pharyngeal projections in healthy volunteers[73]. Tactile-thermal stimulation, another sensory strategy, has also reported a significantly increased bilateral cortical activation after stimulation compared with swallows before stimulation[74] in healthy volunteers, but has not been correlated with changes in swallowing physiology. Hamdy and colleagues have carried out a series of studies focused on the effect of intrapharyngeal sensory electrical stimulation, and found that pharyngeal stimulation is associated with an increase in the pharyngeal motor cortical representation and a decrease in the esophageal representation[75]. fMRI studies have shown that, after one hour of pharyngeal electrical stimulation, the activation of the swallow-related area was increased[35] in healthy subjects. In dysphagic stroke patients, a marked increase in pharyngeal corticobulbar excitability and topographic representation occurred in the undamaged hemisphere compared to the affected hemisphere after pharyngeal stimulation[35]. Two weeks of treatment with transcutaneous electrical stimulation was related to long-term cortical reorganization and swallowing improvement in eight patients with brain damage[41]. However, Gallas *et al*[44] failed to detect changes in the cortical representation following transcutaneous electrical stimulation associated with swallowing improvement.

CONCLUSION

This review explores the effects of several sensory stimulation modalities used on patients with neurogenic oropharyngeal dysphagia and proposes both peripheral and central action mechanisms for these therapies.

Chemical strategies (acidity, pungency, menthol and carbonation) have shown positive effects, improving different swallow parameters of dysphagic patients, although there are few experimental studies. Randomized controlled trials exploring larger populations, the long-term effects, as well as the impact on the clinical outcome of patients are needed. Interestingly, most of the proposed chemical swallow stimulants are agonists of different members of the TRP family. The relationship between TRP and dysphagia opens a new and fascinating

pathway to develop pharmacologic strategies for dysphagia treatment, although much more research is needed in this field. Central effects of chemical stimulants are practically unexplored and there is very little data on the effects of these chemicals in terms of neuroplasticity. The main mechanical stimulus used in the treatment of dysphagia is tactile-thermal stimulation of the faucial pillars but, despite its widespread clinical use, there is little supporting evidence. Results in healthy volunteers indicate that the application of a mechanical stimulus alone or the combination of a mechanical and a thermal (cold) stimulus in the faucial pillars are not enough to modify swallowing physiology, although changes in cortical excitability were found. However, some studies done on dysphagic patients reported positive results. There are a several possible explanations for the discrepant findings. First, the variety of protocols used in the different studies that can lead to discrepant results. Second, the metal probes normally used in tactile-thermal stimulation rapidly increase their temperature once removed from the ice, which can reduce the effect. Finally, the use of healthy volunteers without delayed swallow response could mask any change in swallow physiology. In addition, we hypothesize that the stimulation of the IX cranial nerve alone (which innervates the faucial pillars) is not enough to facilitate swallow and the stimulation of IX and SLN simultaneously is necessary to facilitate the response.

The effect of changing bolus temperature has also been explored in dysphagic patients although only one study explored the effect of a wide range of temperatures on the swallow response of dysphagic patients. The thermal stimuli, like the chemical stimuli are mainly conducted by the TRP channels, but little is known about its central action mechanism.

Finally, electrical stimulation of the pharynx provides the most relevant evidence that sensory stimulation induces cortical neuroplasticity associated with an improvement in the swallow function. It should be noted that in electrical stimulation, as well as in other sensory strategies, frequency, intensity and duration of the stimulus seem to be critical for the final effect, ranging from inhibition to facilitation.

In conclusion, sensory stimulation has become an important emerging therapeutic strategy for dysphagic patients; however, much more research is needed to move from experimental to clinical practice.

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CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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