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Invited Review

A Systematic Review of Reported Methods of Stimulating Swallowing Function and their Classification

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Recent advances in dysphagia treatment have given us many methods of stimulating swallowing function, but no attempt has been made to systematically classify them all. In this review, we provide an exhaustive description of all the techniques and stimulatory substances that stimulate swallowing that have so far been reported in the scientific literature, irrespective of their level of evidence, and we have tried to classify them with the objective of encouraging the future development of research in this direction. The Preferred Reporting Items for Systematic Reviews and Meta-analysis were followed for retrieval of relevant research. A total of 237 records were screened for this literature review. One record was excluded for being published in a language other than English, and 59 articles were excluded for having no original data. Of the 177 records that were assessed for eligibility in this review, 31 were excluded for reasons related to other inclusion and exclusion criteria. Finally, 146 records were classified. We found stimuli related to swallowing published in the literature could be divided into physical and chemical stimuli. Each stimulus had both peripheral and central stimuli when we assessed the main site of action. Physical stimuli included electric, magnetic and thermal stimulations and acupuncture. Chemical stimuli included spices activating transient receptor potential channels, several categories of medications, taste and flavor, and olfactory stimulants. Medications modifying substance P and the dopaminergic system are thought to be peripheral and central stimuli, respectively. This classification may pave the way to discover means to improve swallowing.

Keywords: deglutition; deglutition disorders; electrical; magnetic; stimulants
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Introduction

Although dysphagia (difficult swallowing) can happen to anyone, it is most common in older adults. Approximately 7 to 10 percent of adults older than 50 years have dysphagia, and up to 25 percent of hospitalized patients and 30 to 40 percent of patients in nursing homes experience dysphagia (Brin and Younger 1988; Layne et al. 1989). Since dysphagia is closely related to life-threatening aspiration pneumonia in the elderly, the treatment of dysphagia is one of the most crucial issues in aging societies (Ebihara 2019).

Dysphagia is anatomically divided into oropharyngeal dysphagia and esophageal dysphagia. Patients with oropharyngeal dysphagia typically experience difficulty in the movement of food from the mouth into the pharynx and the esophagus. On the other hand, patients with esophageal dysphagia have difficulty in the passing of the food through the esophagus. Table 1 shows the possible causes of oropharyngeal and esophageal dysphagia (Achem and DeVault 2005; Khan et al. 2014: Clave and Shaker 2015, Wilkinson et al. 2021). Most cases of oropharyngeal dysphagia are caused by functional neuromuscular disorders, particularly cerebrovascular diseases, Parkinson disease and sarcopenia, while most cases of esophageal dysphagia are caused by structural changes, which include changes to the organic

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Table 1. Causes of dysphagia in older people.

Causes of oropharyngeal dysphagia
Neural and muscular causes
Stroke and other cerebrovascular events
Alzheimer's disease and other dementia
Parkinson disease and syndrome
Myasthenia gravis
Amyotrophic lateral sclerosis
Multiple sclerosis
Muscular dystrophy
Dermatomyositis/polymyositis
Sarcopenia
Antipsychotic medication
Structural (passage) causes
Upper esophageal sphincter dysfunction
Head and neck tumors
Zenker's diverticulum
Cricopharyngeal bar/cricopharyngeal achalasia
Osteopytes and other spinal disorders
Prior surgery or radiation therapy
Causes of esophageal dysphagia
Functional causes
Achalasia
Diffuse esophageal spasm
Collagen diseases (e.g., scleroderma, CREST syndrome)
Reflux-related dysmotility
Eosinophilic esophagitis
Hypertensive lower esophageal sphincter
Ineffective esophageal motility disorders
Jackhammer esophagus (Nutcracker esophagus)
Motility disorders due to systemic diseases
Medications
Structural causes
Esophageal rings (e.g., Schatzki rings)
Esophageal webs (e.g., Plummer-Vinson syndrome)
Strictures (e.g., Peptic, medication-induced and others)
Esophageal malignancy
Vascular compression (e.g., Cardiomegaly)
Other extrinsic causes (e.g., mediastinal mass, spinal osteophytes)

structures of the esophagus (Dylczyk-Sommer 2020).

The treatment strategy for dysphagia is chosen based on a number of different factors including diagnosis, prognosis, reaction to compensatory strategies, severity of dysphagia, cognitive status, respiratory function, caregiver support, and patient motivation and interest. Treatment procedures are largely divided into two categories. One category is compensatory treatment procedures, which are designed to change the flow of food/liquids and eliminate symptoms, but do not directly change the physiology of the swallow (Shapiro 2000). Compensatory treatment procedures include postural techniques, food consistency changes, modifying volume and speed of food presentation, and intraoral prosthetics. The other category is therapeutic treatment procedures, which are designed to change and/or improve the physiology of the swallow (Shapiro 2000; Perry et al. 2016). Therapeutic treatment procedures include oral and pharyngeal range-of-motion exercises, resistance exercises, bolus control exercises, swallowing maneuvers, supraglottic swallow, effortful swallow, and the Mendelsohn maneuver. Patients may need a combination of treatment procedures to maintain a safe and nutritionally adequate swallow. For example, postural strategies may be combined with swallowing maneuvers to allow the patient to swallow in a safe and efficient manner.

In recent years, clinical institutions engaged in dyspha-

gia rehabilitation in the form of exercises to restore swallowing function have started combining the standard therapeutic procedures with a range of methods of stimulating swallowing. This has been shown to augment the effectiveness of conventional swallowing training (Sasegbon et al. 2020a). Recent advances in dysphagia treatment have given us many stimulation methods ranging from physical to chemical methods. However, there is little evidence on which swallowing stimulation methods are effective for which type of dysphagia patients. Additionally, no attempt has been made to systematically classify them all.

In this review, in order to organize the currently available knowledge, we provide an exhaustive description of all the techniques and stimulatory substances that stimulate swallowing that have so far been reported in the scientific literature, irrespective of their level of evidence. Then, we tried to systematically classify all the swallowing improvement methods described in the published literature. Although classification is important to compare or analyze things, until now, we did not have a comprehensive classification of all swallowing improvement methods. Using our classification, we expect that the criteria for applying existing swallowing improvement methods can be clarified to some extent. In addition, this classification may pave the way to discover means to improve swallowing and encourage the future development of research in this direction.

Methods

Search strategy

To provide an overview of the evidence on the use of stimulants for swallowing reflex in older people, we undertook a systematic review. We followed a standard protocol in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Page and Moher 2017).

Database searches were conducted in MEDLINE, BIOSIS, EMBASE, and The Cochrane Central Register of Controlled Trials. The initial search was performed with the relevant keywords of “deglutition,” “deglutition disorders,” “swallow,” or “dysphagia” for literature focusing on stimulants for swallowing reflex. Once relevant articles were retrieved, Medical Subject Headings (MeSH) terms and relevant terms were extracted from the article, and used for the further literature search.

The preliminary search results were validated through retrieval of a set of already known relevant articles. Search syntax was customized for each database. The final search syntax is listed in the Appendix 1. All searches were conducted in April 2021.

Included papers were restricted to the English language. No restrictions were made for year of publication or for study designs included in the reviews in order to obtain a complete picture of the effectiveness of the interventions.

Exclusion criteria were articles published in languages other than English and articles not containing original data. Articles with animal experiments were also excluded. Additional articles were identified from the references of the articles in the initial search.

The initial database search identified 554 articles. There was one additional record identified from the references of relevant sources that were not revealed in our original search. After removing duplicated articles, a total of 237 records were screened for this literature review. One record was excluded for being published in a language other than English, and 59 articles were excluded for having no original data. Of the 177 records that were assessed for eligibility in this review, 31 were excluded for reasons related to other inclusion and exclusion criteria. Exclusion criteria were straightforward and were able to be determined directly from the abstracts. Finally, 146 articles remained for analysis and were classified. This process is shown in Fig. 1 of the PRISMA flow diagram.

The detailed search terms and search strategies for all databases are described in the Appendix 1.

Results

Swallowing stimulation methods are broadly divided into those involving physical stimulation and those involving chemical stimulation (Table 2). Physical stimulation techniques include not only electric, magnetic, and thermal methods, but also invasive stimulation methods such as acupuncture. Chemical stimulation includes not only food and beverage modification by spices and flavor, but also systemic oral medication and aromatherapy, which is a form of olfactory stimulation.

Some physical and chemical methods of swallowing stimulation act on the central nervous system, whereas others act peripherally. However, the differences between central and peripheral actions are difficult to distinguish with clarity, as peripheral stimulation activates central nerves associated with swallowing, while central stimulation refreshes the production of peripheral neurotransmitters and renews the sensitivity of peripheral receptors. The peripheral and central nervous systems are constantly in a state of positive or negative feedback, interacting repeatedly in an intimate relationship. In this review, for the purpose of convenience we have classified stimulation methods as peripheral or central depending on their initial main site of action.

Physical stimulation

Methods of physically stimulating the body to encourage swallowing include electromagnetic stimulation, thermal stimulation, and acupuncture. Electromagnetic stimulation acts on both the central and peripheral nervous systems, but thermal stimulation is considered to provide peripheral stimulation whereas acupuncture treatment is regarded as improving swallowing mechanisms via central stimulation (Table 1).

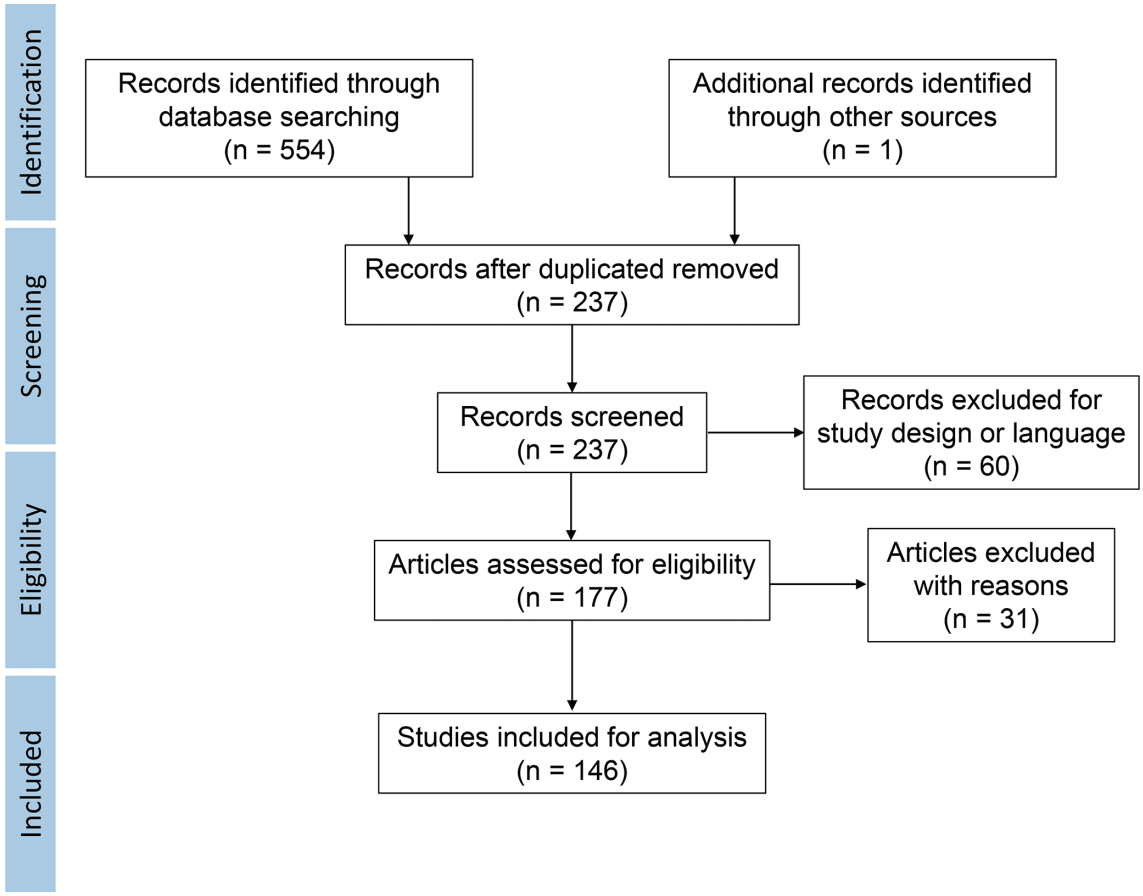

Fig. 1. Flow diagram showing the process of selection of studies for this review.

1. Electrical stimulation and magnetic stimulation

Evidence has recently been collected for the effect of the combined use of electrical and magnetic neuromuscular stimulation devices in augmenting the effectiveness of standard swallowing exercises used in functional dysphagia rehabilitation (Sasegbon et al. 2020a). The main causes of functional dysphagia in the pharyngeal phase of swallowing are muscular weakness and delayed onset of the swallowing reflex. Attempts have long been made to restore muscle strength by applying neuromuscular electric stimulation to cause forced muscle contraction, resulting in the establishment of neuromuscular electrical stimulation (NMES) as the most common stimulation technique in diverse types of dysphagia (Suiter et al. 2006; Bulow et al. 2008; Lim et al. 2009; Park et al. 2009, 2012, 2016, 2018; Permsirivanich et al. 2009; Ryu et al. 2009; Baijens et al. 2012, 2013; Holmes et al. 2012; Heijnen et al. 2012; Long and Wu 2013; Nam et al. 2013; Rofes et al. 2013a; Huang et al. 2014; Toyama et al. 2014; El-Tamawy et al. 2015; Humbert et al. 2015; Song et al. 2015; Terré and Mearin 2015; Zhao et al. 2015; Jing et al. 2016; Langmore et al. 2016; Zhang et al. 2016, 2019; Guillén-Solà et al. 2017; Meng et al. 2018; Sproson et al. 2018; Zeng et al. 2018; Konecny and Elfmark 2018; Bucyana et al. 2019; Poorjavad et al. 2019; Simonelli et al. 2019; Carnaby et al. 2020; Huh et al. 2020; Jeon et al. 2020; Oh et al. 2020; Zhang and Wu 2021; Cola et al. 2021). This technique has been widely reported, with meta-analyses also finding that it improves swallowing function (Carnaby-Mann and Crary 2007; Clark et al. 2009; Chen et al. 2016).

Momosaki et al. (2014) attempted to apply peripheral neuromuscular stimulation using magnetic devises instead of electric ones as repetitive peripheral magnetic stimulation (rPMS). Recently, the usefulness of neuromuscular electrical stimulation and repetitive transcranial magnetic stimulation (rTMS) for post-stroke dysphagia has been reported. However, there is no report that describes the effectiveness of functional magnetic stimulation (FMS) for dysphagia.

Methods of improving the delayed onset of the swallowing reflex include rTMS (Hamdy et al. 1999; Gow et al. 2004; Khedr et al. 2009, 2019; Gallas et al. 2009; Verin and Leroi 2009; Khedr and Abo-Elfetoh 2010; Park et al. 2013, 2017; Drury et al. 2014; Cheng et al. 2015, 2017; Du et al. 2016; Lin et al. 2018; Tarameshlu et al. 2019; Sasegbon et al. 2019, 2020b, 2021; Zhang et al. 2019; Cabib et al. 2020) and transcranial direct current stimulation (tDCS) (Kumar et al. 2011; Yang et al. 2012; Shigematsu et al. 2013; Suntrup et al. 2013; Vasant et al. 2014; Ahn et al. 2017; Cosentino et al. 2018, 2020; Pingue et al. 2018; Suntrup-

Table 2. Classification of swallowing stimuli.

	Principle	Peripheral stimulation	Central stimulation
Physical	Electric	Neuromuscular electrical stimulation (NMES) (¶) Pharyngeal electrical stimulation (PES) (¶¶¶) Transcutaneous electrical sensory stimulation (TESS) (Furuta et al. 2012; Ortega et al. 2016; Maeda et al. 2017; Umay et al. 2017)	Transcranial direct current stimulation (tDCS) (¶¶) Stimulation of the subthalamic nucleus (STN) (Xie et al. 2018)
	Magnetic	Repetitive peripheral magnetic stimulation (rPMS) (Momosaki et al. 2014)	Repetitive traditional magnetic stimulation (rTMS) (†)
	Thermal	Hot (Watando et al. 2004; Michou et al. 2012a) Cold (††)	
	Acupuncture		Traditional Chinese Medicine Theory (†††) Tongue acupuncture (Cai et al. 2015) Nape acupuncture (Li et al. 2016; Liu et al. 2018)
Chemical	Transient receptor potential (TRP) agonists	Capsinoids (§) Ginger (Abe et al. 2015; Hao et al. 2021) Red wine polyphenol (Ebihara et al. 2010) Menthol (Ebihara et al. 2006b; Alvarez-Berdugo et al. 2018) Piperine (Rofes et al. 2014; Alvarez-Berdugo et al. 2018;) Carbonated water (Michou et al. 2012a; Magara et al. 2016; Regan 2020) Sour food/liquid (Regan 2020; Gatto et al. 2021)	
	Medications	Angiotensin-converting enzyme (ACE) inhibitor (Nakayama et al. 1998; Nakashima et al. 2011; Lee et al. 2015) Banxia Houpo Tang (Iwasaki et al. 1999)	L-dopa (Levodopa) (Bayer et al. 1988; Bushmann et al. 1989; Kobayashi et al. 1996; Chen et al. 2017) Theophylline (Ebihara et al. 2004) Cilostazol (Teramoto et al. 2008; Abe et al. 2013) Levetiracetam (Xu et al. 1994)
	Taste and/or Flavor		Sweet (Mistry et al. 2006; Welge-Lussen et al. 2009) Citrus (Hamdy et al. 2003) Flavored-liquid (Babaei et al. 2010)
	Aromatherapy		Black pepper (Ebihara et al. 2006a)

¶, ¶¶, ¶¶¶, †, ††, †††, and § References are summarized in the Appendix 2.

Krueger et al. 2018; Restivo et al. 2019; Erfmann et al. 2020; Li et al. 2020a; Sawan et al. 2020; Wang et al. 2020) to directly increase the excitability of the pharyngeal motor cortex by means of percutaneous stimulation of the cerebral cortex, and the peripheral methods of sensory stimulation of the pharyngeal mucosa or sensory nerves to increase the excitability of the brainstem swallowing center and the pharyngeal motor cortex (Table 1).

Hamdy et al. (1998) showed that electrical stimulation of the pharyngeal mucosa reversibly altered the excitability of the pharyngeal motor cortex. Pharyngeal electrical stimulation (PES) with a catheter electrode was developed on the basis of this evidence, and has been shown to be useful in early recovery from post-stroke dysphagia and other various conditions of dysphagia including post-tracheal intubation (Power et al. 2006; Jayasekeran et al. 2010; Michou et al. 2012b, 2014; Restivo et al. 2013; Suntrup et al. 2015a, b; Bath et al. 2016; Magara et al. 2016; Vasant et al. 2016; Essa et al. 2017; Dziewas et al. 2018; Cabib et al. 2020; Koestenberger et al. 2020). Michou et al. (2014) reported that PES increased the excitability of the pharyngeal motor cortex to a greater extent than did rTMS.

Unlike PES, in which the pharyngeal mucosa is directly stimulated with a catheter electrode, transcutaneous electrical sensory stimulation (TESS) does not require electrode insertion into the pharynx (Furuta et al. 2012; Ortega et al. 2016; Maeda et al. 2017; Umay et al. 2017). When TESS is carried out with an NMES device, the stimulus intensity is set at the sensory threshold level, below the intensity causing muscle contraction (Miller et al. 2013). Based on the hypothesis that TESS reversibly increases the excitability of the pharyngeal motor cortex in the same way as PES, TESS was used in rehabilitation for patients with post-stroke dysphagia (Furuta et al. 2012; Ortega et al. 2016; Maeda et al. 2017; Umay et al. 2017). As for electrical stimuli, there is one report showing an invasive electrical stimulation, stimulation of the subthalamic nucleus (STN), improved dysphagia in patients with Parkinson's

disease (Xie et al. 2018).

2. Thermal stimulation

At what temperature is food easiest to swallow for dysphagia patients? We started investigating this simple question using distilled water (Watando et al. 2004). We inserted a fine catheter through the noses of older individuals in the decubitus position to the level of the palatine uvula, used a syringe attached to the other end of the catheter to inject 1 ml of distilled water at a range of different temperatures, and investigated the association between the temperature of the water when it reached the pharynx and the latency of swallowing reflex onset. Impaired pharyngeal sensation is evident in the prolongation of swallowing reflex latency. The association between the temperature of the injected distilled water and the latency formed a Bell curve, with the latency prolonged to the greatest extent at temperatures similar to body temperature (30°C-40°C), and shorter at temperatures further away from this in either direction (Watando et al. 2004). This showed that either hot or cold food improves swallowing by older people. We thus discovered that even if swallowing function in older people is impaired, they are still sensitive to temperature, and the temperature of the food they consume by mouth is thus equally important in preventing aspiration as its physical nature. The hotter a hot food is, and the colder a cold food, the easier it is for the swallowing reflex to be triggered and the food swallowed. The cold tactile stimulations were widely used for dysphagia rehabilitation (Bove et al. 1998; Hamdy et al. 2003; Watando et al. 2004; Michou et al. 2012a; Elvevi et al. 2014; Cui et al. 2020; Regan 2020; Cola et al. 2021; Gatto et al. 2021) whereas hot temperatures were rarely applied (Watando et al. 2004; Michou et al. 2012a).

Because thermal stimulation is believed to be sensed by transient receptor potential (TRP) thermosensitive receptors located in the free nerve endings of submucosal c-fibers and Aδ-fibers, thermal stimulation is considered to be a peripheral stimulus for swallowing (Ebihara 2019).

3. Acupuncture stimulation

Swallowing function in dysphagia patients is stimulated by acupuncture, a method of treatment used in Chinese traditional medicine, according to reports of its use in post-stroke older patients and those with Parkinson's disease. Acupuncture treatment involves physical stimulation by the insertion of dedicated needles or touching them against the body to stimulate specific sites known as acupuncture points. In most of the studies, acupuncture points used to stimulate the swallowing function were systemically distributed based on traditional Chinese medicine theory (Seki et al. 2005; Chan et al. 2012, 2020; Kikuchi et al. 2014; Zhao et al. 2015, 2019; Lu et al. 2016; Xia et al. 2016; Xiao et al. 2019; Li et al. 2019, 2020b; Wu et al. 2019). Stimulation of these acupuncture points is believed to correct abnormalities in the flow of qi, which follows paths known as meridians (NIH Consensus Statement 1997). Improvement in swallowing as a result of acupuncture treatment is thus unlikely to be the result of direct action on the peripheral nerves that control swallowing, but of a central nervous system mechanism acting via qi. Localized acupuncture such as tongue acupuncture (Cai et al. 2015) and nape acupuncture (Li et al. 2016; Liu et al. 2018) are also based on the theory of qi.

Chemical stimulation

Chemical stimulation can be roughly divided into three types according to the mechanisms of action (Table 1). The first type consists of activators of TRP thermosensitive receptors, which are receptors for temperature-change stimuli. Because these receptors are located in the free nerve endings of the pharyngeal mucosa, such activators are thus peripheral swallowing-stimulating substances. The second type consists of substances that increase substance P, which is associated with axonal reflexes. Substance P is known to induce the swallowing and coughing reflexes, and is believed to act as a neurotransmitter in pharyngeal mucosal stimulation, with increased localized substance P acting as a peripheral swallowing stimulation. The third type consists of chemical substances that activate the dopamine system, as increased dopamine levels in the basal ganglion and other areas of the brain are believed to promote swallowing, and this constitutes central stimulation.

The characteristics of aromatherapy mean that this is also considered to be central stimulation (Table 1).

1. TRP agonists

Although a difference between food temperature and body temperature encourages the swallowing reflex, constantly providing food at such temperatures is not easy. It is thought that when sensing the temperature of the outside world, peripheral sensory nerves convert temperature stimuli into electrical signals and transmit this information to the central nervous system. In this process, receptors that only react to a specific temperature are present at sites including the neuronal membrane surface (Clapham 2003). Molecules known to be implicated in temperature reception in mammals include the six TRP channels on the peripheral nerve surface (TRPV1, TRPV2, TRPV3, TRPV4, TRPM8, and TRPA1), each of which is activated at a different temperature (TRPV1 > 43°C, TRPV2 > 52°C, TRPV3 > 32°C-39°C, TRPV4 > 27°C-35°C, TRPM8 > 25°C-28°C, and TRPA1 > 17°C) (Clapham 2003). The temperature ranges at which the swallowing reflex is activated suggest that of these six thermosensitive TRP channels, TRPV1, TRPV2, TRPM8, and TRPA1 may be involved in activating the swallowing reflex (Ebihara and Ebihara 2011). In fact, some natural foodstuffs, particularly spices, are agonists of these thermosensitive receptors, and these may hold potential as medications to promote swallowing (Kittipanya-Ngam et al. 2021).

Capsaicin and other capsinoids have been reported to

promote the swallowing reflex and improve swallowing function as TRPV1 agonists (Ebihara et al. 1993, 2005; Yamasaki et al. 2010; Rofes et al. 2013b; Ortega et al. 2016; Kondo et al. 2017; Nakato et al. 2017; Alvarez-Berdugo et al. 2018; Tomsen et al. 2019; Wang et al. 2019; Cabib et al. 2020; Suntrup-Krueger et al. 2021). Ginger is another spice which is reported to improve swallowing function via TRPV1 receptors (Abe et al. 2015; Hao et al. 2021). Although they do not directly stimulate TRPV1, red wine polyphenols have also been reported to act to improve the swallowing reflex by intensifying the reaction of TRPV1 receptors (Ebihara et al. 2010). The TRPM8 agonist menthol (Ebihara et al. 2006b; Alvarez-Berdugo et al. 2018) and the TRPA1 agonist piperine (Rofes et al. 2014; Alvarez-Berdugo et al. 2018) have also been reported to promote the swallowing reflex and swallowing function. However, it must be noted that these thermosensitive TRP receptors may not themselves be the switch that initiates the swallowing reflex, and that the swallowing reflex is not induced by these stimuli alone.

Oral chemesthesis induced by carbonated beverages (Michou et al. 2012a; Magara et al. 2016; Regan 2020) and sour liquids (Regan 2020; Gatto et al. 2021) was reported to accelerate swallowing responses, and is thought to act on common somesthetic receptors with TRP agonists.

2. Medications that increase substance P at the periphery

Substance P is distributed throughout the peripheral nerves in the digestive system, and is believed to be a peripheral nervous system neurotransmitter for swallowing (Niel 1991; Jin et al. 1994). It is also known to function as a neurotransmitter in local pharyngeal stimulation (Yoshida et al. 2000; Renner et al. 2013). A decrease in the concentration of substance P in the pharyngeal mucosa has been shown to lead to a decline in swallowing function (Jin et al. 1994; Niimi et al. 2018; Schroder et al. 2019) and increasing the concentration of substance P in the pharynx by some means would improve swallowing function.

Angiotensin-converting enzyme (ACE) inhibitors, which are antihypertensive agents, inhibit ACE. ACE not only cleaves angiotensin I, but also the analogous peptide substance P. Accordingly, ACE inhibitors not only inhibit the synthesis of active angiotensin II, but also prevent the breakdown of substance P, increasing the latter's activity. Because substance P in peripheral sensory nerves is a neurotransmitter for the swallowing reflex, this has the effect of improving the swallowing response (Nakayama et al. 1998; Nakashima et al. 2011; Lee et al. 2015). In fact, many studies have shown that taking ACE inhibitors regularly reduces the risk of pneumonia (Sekizawa et al. 1998; Okaishi et al. 1999; Liu et al. 2012; Lee et al. 2015). Systematic review and meta-analysis also reported that it has a significant inhibitory effect on pneumonia (Caldeira et al. 2012).

Banxia houpo tang is a traditional Chinese medication that is described in the Chin-kuei-yao-lüeh classic of Chinese traditional medicine as being used to treat foreign-body sensation in the throat. This expression is often used in traditional Chinese medicine to describe choking because the movement of the pharyngeal vault has become clumsy due to age or other reasons. Iwasaki et al. (1999) reported that banxia houpo tang improves the swallowing reflex by increasing the concentration of substance P in saliva. The routine use of banxia houpo tang has also been shown to suppress the occurrence of pneumonia in older people with dementia (Iwasaki et al. 2007).

3. Medications that activate the dopamine system in the central nervous system

The synthesis of substance P, a peripheral neurotransmitter for the swallowing reflex, is regulated upstream by the dopamine nervous system, and basal ganglion damage reduces the number of dopamine receptors, reducing the release of substance P (Yamaya et al. 2001). In Parkinson's disease, which damages the dopamine nerves, the concentration of substance P in saliva decreases and swallowing function becomes impaired (Schroder et al. 2019). Animal experiments have also found that dopamine receptor knockout mice become unable to swallow (Xu et al. 1994). Based on these findings, a series of mechanisms is envisaged whereby cerebrovascular injury such as a basal ganglion infarction or Parkinson's disease impairs the function of the dopamine nervous system, leading to a lack of substance P that delays the swallowing reflex and causes dysphagia (Yamaya et al. 2001). Therefore, medications that activate the dopamine system in the basal ganglion or elsewhere in the central nervous system may promote swallowing.

Parkinson's disease drugs that activate the dopamine system have promise as medications to promote swallowing. Dopamine does not pass through the blood-brain barrier (BBB), but the dopamine precursor L-dopa passes through the BBB to reach the brain, where it is converted into dopamine by dopa-decarboxylase (DDC), and L-dopa has also been reported to promote the swallowing reflex (Bayer et al. 1988; Bushmann et al. 1989; Kobayashi et al. 1996; Chen et al. 2017).

The bronchodilator theophylline blocks the inhibitory neurotransmitter adenosine from binding to A2 receptors at concentrations lower than those required to dilate the bronchi. A2 receptors are numerous on dopaminergic nerves, and this inhibitory action of theophylline causes dopamine nerve disinhibition, which is speculated to improve the swallowing reflex by activating dopamine nerves in the basal ganglion and elsewhere (Ebihara et al. 2004).

The phosphodiesterase III inhibitor cilostazol is both an antiplatelet agent and known to increase cerebral perfusion, and is widely used in the treatment of cerebral infarction. Cilostazol improves swallowing responses (Teramoto et al. 2008; Abe et al. 2013). The mechanism reportedly consists of the activation by cilostazol of cAMP responsive element binding protein, which maintains the function of tyrosine hydroxylase, a dopamine synthetase, and increases dopamine production in the nigrostriatal system (Zhang et

al. 2009). The treatment of chronic-phase post-stroke patients with cilostazol has been reported to prevent pneumonia (Shinohara 2006).

Levetiracetam, an antiepileptic drug, is reported to be effective in the rehabilitation treatments of dysphagia due to stroke (Xu et al. 1994). In an animal seizure model, pretreatment of levetiracetam compensated decline of dopamine (Al-Shorbagy et al. 2013). Sweet taste (Mistry et al. 2006; Welge-Lussen et al. 2009), citrus (Hamdy et al. 2003) and flavored-liquid (Babaei et al. 2010) stimulated swallowing response in healthy subjects. These kinds of reward signals are primarily coded by dopamine, which modulates the synaptic connections of neurons in the striatum (Yagishita et al. 2014).

4. Aromatherapy with black pepper essential oil

Residents of a care home for older people were arbitrarily assigned to three groups to receive aromatherapy with black pepper, lavender, or no aroma. They received olfactory stimulation from a piece of filter paper soaked in black pepper essential oil, lavender essential oil, or distilled water for 1 minute before every meal for 1 month. Measurements of the swallowing reflex and substance P concentration in peripheral blood before and after the olfactory stimulation intervention showed that the swallowing reflex improved substantially after stimulation with the smell of black pepper (Ebihara et al. 2006a). At the same time, the concentration of substance P in the blood also rose significantly. These changes were not observed in either the lavender or the control group. Olfactory stimulation with black pepper essential oil has been found to directly activate the insular cortex, which is important in the cortical regulation of swallowing (Ebihara et al. 2006a). This method of improving the swallowing reflex by aromatherapy with black pepper can be used even for patients in a very poor state, and is therefore considered to be extremely promising for dysphagia treatment and aspiration pneumonia prevention.

Discussion

In this systemic review, we found stimuli related to swallowing that have been published in the literature and classified them into physical and chemical stimuli. Each stimulus had both peripheral and central stimuli when we assessed the main site of action. Physical stimuli included electric, magnetic and thermal stimulations and acupuncture. Chemical stimuli included spices activating TRP channels, several categories of medications, taste and flavor, and olfactory stimulants. The existence of various methods means that there is no definitive way to improve swallowing. Therefore, by classifying the stimuli, we hoped to find clues for the development of new swallowing improvement methods.

Pharyngeal touch is a sense that acts as a peripheral mechanism of pharyngeal perception, and this is considered to be one of the most important sensory receptors associated with swallowing. From a range of histological findings, it is believed that organs with touch receptors of the same or similar structure to those of glabrous skin are responsible for sensing touch in the pharyngeal mucosa. The most important receptor organs that perceive touch stimuli in glabrous skin are Meissner's corpuscles, Merkel cells, Pacinian corpuscles, and Ruffini endings, and these or similar structures are believed also to be present in the pharyngeal mucosa (Alvarez-Berdugo et al. 2016a). In addition to these touch-sensitive receptors, the pharyngeal mucosa also contains free nerve endings as separate, independent nerves. These free nerve endings contain TRP thermosensitive receptors that are sensitive to thermal and chemical stimuli (Alvarez-Berdugo et al. 2016b). With aging, morphological changes in the peripheral receptors and other abnormalities of the sensory systems, such as detection thresholds, nerve conduction velocities, structural changes of sensory fibers and decrease in nerve fiber density, occur (Decorps et al. 2014). These influences are also considered to be involved in attenuation of sensation and sensitivity in the elderly. In order to develop effective treatment for dysphagia, pharyngeal sensation is a pivotal target.

Merkel cells are the most abundant of these organs in the oropharynx, and their number is known to decrease with age (Moayedi et al. 2018). The touch receptors on the surface of the cell membrane of Merkel cells are Piezo2 channels, and the effective stimulation of these Piezo2 receptors is thought to be necessary to preserve pharyngeal perception (Ranade et al. 2014). In recent years, a succession of reports has shown that Piezo2 receptor sensitivity is modified by changes in a range of different intracellular signal transduction mechanisms (Sonekatsu et al. 2019; Del Rosario et al. 2020). Swallowing stimulation techniques based on these Piezo2 receptors may be developed in future. Future studies revealing other molecular mechanisms of pharyngeal sensation are warranted to prevent aspiration pneumonia.

Due to the nature of our search strategy for swallowing stimulations, the methods in Table 2 are expected to be useful for oropharyngeal dysphagia, particularly for neural and muscular causes, rather than esophageal dysphagia. Regardless of peripheral or central stimuli, and physical or chemical stimuli, all these methods may be effective for oropharyngeal dysphagia due to the neural and muscular causes shown in Table 1 because the methods may facilitate the neuromuscular circuit of swallowing responses even if the particular pathways are damaged (Ebihara and Ebihara 2011). However, which of the methods presented in Table 2 is more effective for which type of neural and muscular diseases is an issue for future investigations. Although many studies in Table 2 investigated cerebrovascular diseases, that does not indicate that the methods used were ineffective against other diseases.

When pharyngeal dysphagia is complicated by esophageal dysphagia, it seems that caution should be exercised when using TRP agonist. Both TRPV1 and TRPA1 ago-

nists were reported to activate inflammatory nociception in the esophagus and worsen the symptoms of reflux-diseases (Yu et al. 2016). Therefore, capsinoids, ginger, piperine, carbonated water and sour foods/liquids should not be used if esophageal dysphagia coexists with pharyngeal dysphagia**.** On the other hand, menthol, a TRPM8 agonist, is reported to relieve gastroesophageal reflux-induced symptoms and reduce upper esophageal pressure (Zhang et al. 2020; Lei et al. 2021), suggesting beneficial usage of menthol in patients with a combination of both oropharyngeal and esophageal dysphagia. However, there are few studies on the combination of pharyngeal dysphagia and esophageal dysphagia. Further studies in this area are needed.

The present review has limitations. First, it is possible that not all studies describing how to improve swallowing could be identified. We noticed that letter-style papers without abstracts are hard to find in literature searches, and there are many such papers, including ours. Second, peripheral and central classifications may have unclear boundaries. More specifically, some may be critical of classifying acupuncture as central. The mechanism of action of acupuncture cannot be explained by Western medicine, but it seems to be at least a systemic mechanism.

In this review, we showed an example classification of swallowing improvement methods. We cannot compare or analyze things without classification. However, it is also important not to think about classification in a fixed manner. Although classifications can facilitate the comparison and analysis of things, it is important to avoid thinking about classifications in a fixed manner. In other words, trying to see the relationships between things in a more multidimensional way is also important for the improvement of dysphagia treatment.

Conclusions

The current methods to improve swallowing function in dysphagia can be categorized in a 2 × 2 table such as a matrix of peripheral vs. central and physical vs. chemical stimuli. Peripheral or central were classified depending on their initial main site of action. In the physical method, electrical and magnetic stimuli have both peripheral and central means. Thermal stimuli and acupuncture are thought to be peripheral and central physical stimuli, respectively. In chemical stimuli, TRP agonists are thought to be peripheral stimuli and taste, flavor and aromatherapy are thought to be central stimuli. Medications modifying substance P and dopaminergic system are thought to be peripheral and central stimuli, respectively.

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Conflict of Interest

The authors declare no conflict of interest.

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Appendix 1

Search syntax

#1 (mh "DEGLUTITION") or (mh "DEGLUTITION DISORDERS") or DEGLUTIT* or SWALLOW* or DYSPHAG*

#2 NMES OR (NEUROMUSCUL* near/2 ELECTRIC* near/2 STIMULAT*) or TESS OR PES OR TDCS

#3 RPMS OR RTMS or pms or tms

#4 (HIGH OR LOW) near/2 TEMPERATUR*

#5 (mh "ACUPUNCTURE THERAPY") or ACUPUNCTUR* or ZUSANLI OR TAIXI

#6 (mh "TOOTHBRUSHING") or TOOTHBRUSH* OR (TOOTH near/2 BRUSH*) OR (ORAL OR MOUTH) near/3 (CARE OR HYGIEN*)

#7 (TRP OR [TRANSIENT near/2 RECEPTOR near/2 POTENTIAL]) near/2 CHANNEL* near/2 STIMULAT*

#8 CAPSAICIN* OR CAPSIAT*

#9 MENTHOL OR MENTHOLS

#10 PIPERINE

#11 ([mh "POLYPHENOLS"] or POLYPHENOL*) AND {REDWIN* OR (RED near/2 [WINE OR WINES])}

#12 (mh "ANGIOTENSIN-CONVERTING ENZYME INHIBITORS") or ACEI or (ACE near/1 Inhibitor*) OR (ANGIOTENSIN* near/2 CONVERT* OR KININASE* near/2 [II OR 2]) near/2 (INHIBITOR* OR ANTAGONIST* OR BLOCKER*)

#13 CAPTOPRIL* OR ALACEPRIL* OR LISINOPRIL* OR IMIDAPRIL* OR QUINAPRIL* OR TEMOCAPRIL* OR DELAPRIL* OR BENAZEPRIL* OR CILAZAPRIL* OR TRANDOLAPRIL* OR ENALAPRIL* OR PERINDOPRIL* OR FOSINOPRIL* OR MOEXIPRIL* OR RAMIPRIL* OR SPIRAPRIL* OR ZOFENOPRIL*

#14 BANXIA near/2 HOUPO near/2 TANG

#15 (L NEXT DOPA) OR LDOPA OR LEVODOPA OR ROTIGOTIN* OR AMANTADIN* OR THEOPHYLLIN* OR CILOSTAZOL* OR FOLAT* OR FOLIC NEXT ACID OR FERULIC NEXT ACID OR CANNABINOID*

#16 (BLACK near/2 [PEPPER OR PIPER]) AND (ESSENTIAL near/2 OIL)

#17 STIMULAT* or #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16

#18 #1 and #17

#19 (mh DEGLUTITION[mj]) or (mh "DEGLUTITION DISORDERS"[mj]) or (DEGLUTIT* or SWALLOW* or DYSPHAG*): ti

#20 #18 and #19

#21 (NMES OR [NEUROMUSCUL* near/2 ELECTRIC* near/2 STIMULAT*] or TESS OR PES OR TDCS): ti, ab

#22 RPMS OR RTMS or pms or tms

#23 ([HIGH OR LOW] near/2 TEMPERATUR*): ti, ab

#24 (mh "ACUPUNCTURE THERAPY"[mj]) or (ACUPUNCTUR* or ZUSANLI OR TAIXI): ti, ab

#25 (mh "TOOTHBRUSHING"[mj]) or (TOOTHBRUSH* OR [TOOTH near/2 BRUSH*] OR [ORAL OR MOUTH] near/3 [CARE OR HYGIEN*]): ti, ab

#26 {(TRP OR [TRANSIENT near/2 RECEPTOR near/2 POTENTIAL]) near/2 CHANNEL* near/2 STIMULAT*}: ti, ab

#27 (CAPSAICIN* OR CAPSIAT*): ti, ab

#28 (MENTHOL OR MENTHOLS): ti, ab

#29 PIPERINE: ti, ab

#30 {(mh "POLYPHENOLS"[mj]] or POLYPHENOL*: ti, ab) AND {REDWIN* OR (RED near/2 [WINE OR WINES])}: ti, ab

#31 (mh "ANGIOTENSIN-CONVERTING ENZYME INHIBITORS"[mj]) or {ACEI or (ACE near/1 Inhibitor*) OR (ANGIOTENSIN* near/2 CONVERT* OR KININASE* near/2 [II OR 2]) near/2 (INHIBITOR* OR ANTAGONIST* OR BLOCKER*)}: ti, ab

#32 (CAPTOPRIL* OR ALACEPRIL* OR LISINOPRIL* OR IMIDAPRIL* OR QUINAPRIL* OR TEMOCAPRIL* OR DELAPRIL* OR BENAZEPRIL* OR CILAZAPRIL* OR TRANDOLAPRIL* OR ENALAPRIL* OR PERINDOPRIL* OR FOSINOPRIL* OR MOEXIPRIL* OR RAMIPRIL* OR SPIRAPRIL* OR ZOFENOPRIL*): ti, ab

#33 (BANXIA near/2 HOUPO near/2 TANG): ti, ab

#34 ([L NEXT DOPA] OR LDOPA OR LEVODOPA OR ROTIGOTIN* OR AMANTADIN* OR THEOPHYLLIN* OR CILOSTAZOL* OR FOLAT* OR FOLIC NEXT ACID OR FERULIC NEXT ACID OR CANNABINOID*): ti, ab

#35 (BLACK near/2 [PEPPER OR PIPER]): ti, ab AND (ESSENTIAL near/2 OIL): ti, ab
#36 STIMULAT*: ti, ab or #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35
#37 #20 AND #36
#38 #37 and (DEGLUTIT* or SWALLOW* or DYSPHAG*): ti and stimula*: ti, ab, kw

*in the syntax indicates that the symbol was used for prefix searches.

Appendix 2

References cited by ¶, ¶¶, ¶¶¶, †, ††, ††† and § in Table 2.

(¶) (Suiter et al. 2006; Bulow et al. 2008; Lim et al. 2009; Park et al. 2009, 2012, 2016, 2018; Permsirivanich et al. 2009; Ryu et al. 2009; Baijens et al. 2012, 2013; Holmes et al. 2012; Heijnen et al. 2012; Long and Wu 2013; Nam et al. 2013; Rofes et al. 2013; Huang et al. 2014; Toyama et al. 2014; El-Tamawy et al. 2015; Humbert et al. 2015; Song et al. 2015; Terré and Mearin 2015; Zhao et al. 2015; Jing et al. 2016; Langmore et al. 2016; Zhang et al. 2016, 2019; Guillén-Solà et al. 2017; Meng et al. 2018; Sproson et al. 2018; Zeng et al. 2018; Konecny and Elfmark 2018; Bucyana et al. 2019; Poorjavad et al. 2019; Simonelli et al. 2019; Carnaby et al. 2020; Huh et al. 2020; Jeon et al. 2020; Oh et al. 2020; Zhang and Wu 2021; Cola et al. 2021)

(¶¶) (Kumar et al. 2011; Yang et al. 2012; Shigematsu et al. 2013; Suntrup et al. 2013; Vasant et al. 2014; Ahn et al. 2017; Cosentino et al. 2018, 2020; Pingue et al. 2018; Suntrup-Krueger et al. 2018; Restivo et al. 2019; Erfmann et al. 2020; Li et al. 2020a; Sawan et al. 2020; Wang et al. 2020)

(¶¶¶) (Power et al. 2006; Jayasekeran et al. 2010; Michou et al. 2012b, 2014; Restivo et al. 2013; Suntrup et al. 2015a, b; Bath et al. 2016; Magara et al. 2016; Vasant et al. 2016; Essa et al. 2017; Dziewas et al. 2018; Cabib et al. 2020; Koestenberger et al. 2020)

(†) (Hamdy et al. 1999; Gow et al. 2004; Khedr et al. 2009, 2019; Gallas et al. 2009; Verin and Leroi 2009; Khedr and Abo-Elfetoh 2010; Park et al. 2013, 2017; Drury et al. 2014; Cheng et al. 2015, 2017; Du et al. 2016; Lin et al. 2018; Tarameshlu et al. 2019; Sasegbon et al. 2019, 2020b, 2021; Zhang et al. 2019; Cabib et al. 2020)

(††) (Bove et al. 1998; Hamdy et al. 2003; Watando et al. 2004; Michou et al. 2012a; Elvevi et al. 2014; Cui et al. 2020; Regan 2020; Cola et al. 2021; Gatto et al. 2021)

(†††) (Seki et al. 2005; Chan et al. 2012, 2020; Kikuchi et al. 2014; Zhao et al. 2015, 2019; Lu et al. 2016; Xia et al. 2016; Xiao et al. 2019; Li et al. 2019, 2020b; Wu et al. 2019)

(§) (Ebihara et al. 1993, 2005; Yamasaki et al. 2010; Rofes et al. 2013b; Ortega et al. 2016; Kondo et al. 2017; Nakato et al. 2017; Alvarez-Berdugo et al. 2018; Tomsen et al. 2019; Wang et al. 2019; Cabib et al. 2020; Suntrup-Krueger et al. 2021)