Japanese Dental Science Review 59 (2023) 421–430

Contents lists available at ScienceDirect

Japanese Dental Science Review

journal homepage: www.elsevier.com/locate/jdsr

Transient receptor potential channels as an emerging therapeutic target for oropharyngeal dysphagia

Mohammad Zakir Hossain *, Junichi Kitagawa *

Department of Oral Physiology, School of Dentistry, Matsumoto Dental University, Shiojiri, Japan

ARTICLE INFO

Keywords:
TRP channels
Swallowing
Oropharyngeal dysphagia
TRP channel agonist
Neuroplasticity

ABSTRACT

Oropharyngeal dysphagia is a serious health concern in older adults and patients with neurological disorders. Current oropharyngeal dysphagia management largely relies on compensatory strategies with limited efficacy. A long-term goal in swallowing/dysphagia-related research is the identification of pharmacological treatment strategies for oropharyngeal dysphagia. In recent decades, several pre-clinical and clinical studies have investigated the use of transient receptor potential (TRP) channels as a therapeutic target to facilitate swallowing. Various TRP channels are present in regions involved in the swallowing process. Animal studies have shown that local activation of these channels by their pharmacological agonists initiates swallowing reflexes; the number of reflexes increases when the dose of the agonist reaches a particular level. Clinical studies, including randomized clinical trials involving patients with oropharyngeal dysphagia, have demonstrated improved swallowing efficacy, safety, and physiology when TRP agonists are mixed with the food bolus. Additionally, there is evidence of plasticity development in swallowing-related neuronal networks in the brain upon TRP channel activation in peripheral swallowing-related regions. Thus, TRP channels have emerged as a promising target for the development of pharmacological treatments for oropharyngeal dysphagia.

1. Introduction

Oropharyngeal dysphagia is a common problem in older adults and patients with neurological/neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, dementia, or multiple sclerosis), neuromuscular problems (e.g., myasthenia gravis), and neurovascular accidents (e.g., stroke or traumatic brain injury) [1–8]. It is often associated with sarcopenia, malnutrition, and dehydration [1,9–15].

Individuals with oropharyngeal dysphagia exhibit abnormalities or difficulties in transporting the food bolus from the oral cavity to the esophagus [16–18]. They often experience a delay in swallow initiation, leading to impaired swallowing safety because of the penetration or aspiration of food particles or liquids into the laryngeal vestibule, airways, or lungs [9,19]. This impaired swallowing safety is often associated with delay in laryngeal vestibule closure, delay in upper esophageal sphincter opening, and slowed hyoid motion [20–22]. Studies have shown that > 50% of all patients with oropharyngeal dysphagia exhibit impaired swallowing safety because of bolus penetration or aspiration into the airway [20,23]. The aspiration of food particles or liquids can lead to aspiration pneumonia. Furthermore, patients with oropharyngeal dysphagia often experience a sensation that food is stuck in the throat or mouth because of weak bolus propulsion force and impaired pharyngeal clearance, which lead to bolus residues in oropharyngeal regions after swallowing [24,25].

Current management of oropharyngeal dysphagia in clinics largely relies on compensatory strategies, including modification of food viscosity, texture, or volume [4,21,23,26–28]. Various swallowing-related postures, exercises, or maneuvers (e.g., chin tuck or head tilt) are often prescribed [29]. Although these compensatory strategies are intended to counteract swallowing difficulty, they display limited efficacy in terms of restoring impaired swallowing physiology [4,21,23,26–28,30]. There is no established pharmacological treatment for oropharyngeal dysphagia [31–34]. In recent decades, several pharmacological strategies have been studied in swallowing or dysphagia-related research, including angiotensin-converting enzyme inhibition, calcium channel blockade, acetylcholinesterase enzyme inhibition, use of dopaminergic agents, and TRP channel targeting [31,33]. Among these strategies, TRP channel targeting is the most promising in terms of facilitating swallowing function [31–35]. A recent meta-analysis of randomized

* Corresponding authors.
E-mail addresses: mohammad.zakir.hossain@mdu.ac.jp (M.Z. Hossain), junichi.kitagawa@mdu.ac.jp (J. Kitagawa).

https://doi.org/10.1016/j.jdsr.2023.09.002
Received 3 July 2023; Received in revised form 10 September 2023; Accepted 25 September 2023

controlled clinical trials showed that, in patients with neurogenic dysphagia, treatment involving TRP channel targeting yielded a large, statistically significant effect size (magnitude of difference in outcomes) compared with placebo interventions [33]. The pooled effect size of treatment with other pharmacological agents was not statistically significant. Animal studies revealed dose-dependent facilitation of the swallowing reflex by agonists of various TRP channels [32,36–38]. Therefore, TRP channel targeting is a promising strategy for the development of pharmacological therapeutics for oropharyngeal dysphagia [31–33]. The present narrative review discusses recent advancements in TRP channel targeting research to facilitate swallowing function, including possible underlying neurophysiological mechanisms.

2. TRP channels and their presence in peripheral swallowing-related regions

TRP channels are non-selective cation channels that function as cellular sensors for a broad range of physical and chemical stimuli [39–42]. Most of the TRP channels are permeable to Ca^{2+}. Some are also permeable to other cations (e.g., Na^{+} and Mg^{2+}). Thus far, 28 types of TRP channels have been identified in mammals [39,40]. They are categorized into six subfamilies: TRPA (ankyrin), TRPC (canonical), TRPM (melastatin), TRPML (mucolipin), TRPP (polycystin), and TRPV (vanilloid). Some of these subfamilies have several members: six in the TRPV subfamily (TRPV1–6), seven in the TRPC subfamily (TRPC1–7), eight in the TRPM subfamily (TRPM1–8), three in the TRPML subfamily (TRPML1–3), and three in the TRPP subfamily (TRPP1–3) [39,40]. Several types of TRP channels have been detected in peripheral swallowing-related regions in animals and humans (Table 1). They are primarily located on nerve fibers and in epithelial cells; they are also expressed in other structures (e.g., fibroblast-like cells, taste bud cells, vascular endothelial cells, and sensory corpuscles).

3. TRP channel expression patterns on afferent neurons that innervate swallowing-related regions

TRP channels are also detected in swallowing-related ganglia (e.g., nodose, petrosal, jugular, and trigeminal ganglia), which contain the cell bodies of afferent neurons that innervate peripheral swallowing-related regions [36–38,44,59,62,63]. Researchers have identified afferent neurons in ganglia by injecting retrograde tracers into peripheral swallowing-related regions or incorporating tracers into the cut ends of nerves innervating those regions [36–38,44,59,62]. Those studies revealed that TRP channels were expressed on various percentages of retrograde-traced afferent neurons innervating peripheral swallowing-related regions (Table 2).

The presence of TRP channels in peripheral swallowing-related regions and on afferent neurons innervating those regions provides a rationale for utilizing TRP channels to facilitate swallowing.

4. TRP channel targeting to improve swallowing function

Several pre-clinical and clinical studies demonstrated promising results in terms of swallowing function when TRP channels were targeted in peripheral swallowing-related regions.

4.1. TRP channel activation facilitates initiation of swallowing reflexes in animals

Pre-clinical studies have examined the effects of topical application of TRP agonists/activators in peripheral swallowing-related regions to initiate swallowing reflexes (Table 3) [32,36–38,65–70]. The activation of a particular TRP channel by its agonist led to initiation of swallowing reflex; the number of reflexes increased when the dose of the agonist increased [32,36–38]. Topical application of an antagonist for a particular channel before application of the agonist significantly

Table 1
Locations of various TRP channels in peripheral swallowing-related regions.

TRP channels	Regions	Locations	Species	Ref.
TRPV1	Oropharynx and larynx (tongue, pharynx, and epiglottis)	Epithelial cells Nerve fibers (submucosa) Vascular endothelial cells	Human	[43]
	Pharynx, epiglottis, soft palate, and larynx	Nerve fibers (intraepithelial and subepithelial) Taste bud-like structures	Rats	[44]
	Larynx (epiglottic area)	Epithelial cells, Nerve fibers (subepithelial, lamina propria)	Human	[45]
	Larynx (epiglottis, vocal fold, arytenoid, subglottic, and tracheal areas)	Nerve fibers (intraepithelial, subepithelial) Epithelial cells	Mice	[46]
	Larynx	Nerve fibers (subepithelial) Intralaryngeal ganglia	Rats	[47]
	Larynx (epiglottis, arytenoid, glottis, and subglottis)	Nerve fibers (intraepithelial and subepithelial) Epithelial cells Intra- and subgemmal nerve plexus of taste buds Nerve fibers around the laryngeal glands	Rats	[48]
	Nasal cavity	Epithelial cells Vascular endothelial cells Submucosal glands Nerve fibers (submucosa)	Human	[49]
	Trachea	Nerve fibers (intraepithelial, subepithelial, around the blood vessels, and muscle)	Rats	[50]
	Oral cavity (tongue and palate)	Nerve fibers (within taste papillae), Epithelial cells	Rats	[51]
	Tongue	Nerve fibers	Rats	[52]
	Oral cavity (tongue and hard palate)	Nerve fibers (intraepithelial and subepithelial) End bulbs of Krause	Human	[53]
TRPV2	Pharynx, epiglottis, the root of the tongue, and soft palate	Dendritic cells Nerve fibers	Rats	[44]
	Trachea	Nerve fibers (mainly subepithelial) Some epithelial cells	Rats	[50]
	Larynx	Nerve fibers (intraepithelial and subepithelial) Intralaryngeal ganglia	Rats	[47]
	Larynx	Nerve fibers (intraepithelial and subepithelial) Intralaryngeal ganglia	Rats	[54]
	Larynx (epiglottis, arytenoid, glottis, and subglottis)	Nerve fibers (intraepithelial and subepithelial) Epithelial cells Intra- and subgemmal nerve plexus of taste buds Nerve fibers around the laryngeal glands	Rats	[48]

(*continued on next page*)

Table 1 (*continued*)

TRP channels	Regions	Locations	Species	Ref.
	Larynx (epiglottis, vocal fold, arytenoid, subglottic, and tracheal areas)	Epithelial cells Nerve fibers (mainly subepithelial)	Mice	[46]
	Larynx (epiglottic area)	Epithelial cells Nerve fibers (mainly subepithelial)	Human	[45]
TRPV3	Larynx (epiglottis, vocal fold, arytenoid, subglottic, and tracheal areas)	Epithelial cells	Mice	[46]
	Larynx (epiglottic area)	Epithelial cells, Nerve fibers, Glands	Human	[45]
	Larynx (epiglottis, arytenoid, aryepiglottic folds, glottis, and subglottis)	Epithelial cells Taste bud-like structures	Mice	[55]
	Larynx (arytenoid, subglottic, proximal esophageal, and tracheal areas)	Epithelial cells	Human	
	Oral cavity (tongue and hard palate)	Epithelial cells	Human	[53]
TRPV4	Pharynx	Nerve fibers Periaxonic cells (presumably Schwann cells and fibroblasts)	Human	[56]
	Laryngopharynx and associated laryngeal regions	Nerve fibers	Rats	[38]
	Larynx (epiglottis, vocal fold, arytenoid, subglottic, and tracheal areas)	Epithelial cells, laryngeal glands	Mice	[46]
	Larynx (epiglottic area)	Epithelial cells, Glands	Human	[45]
	Larynx (epiglottis, arytenoid, aryepiglottic folds, glottis, and subglottis)	Epithelial cells Taste bud-like structures	Mice	[55]
	Larynx (arytenoid, subglottic, proximal esophageal, and tracheal areas)	Epithelial cells	Human	
	Tongue	Epithelial cells Taste papillae Taste bud cells (type IV)	Mice	[57]
	Esophagus	Epithelial cells	Mice	
	Oral cavity (tongue and hard palate)	Epithelial cells	Human	[53]
TRPA1	Laryngopharynx and associated laryngeal regions	Nerve fibers (mainly subepithelial) Fibroblast-like cells	Rats	[36]
	Oropharynx and larynx (tongue, pharynx, and epiglottis)	Fibroblast-like cells	Human	[43]
	Oral cavity (tongue and hard palate)	Fibroblasts Immune cells Nerve fibers	Human	[53]
TRPM8	Oropharynx (tongue, pharynx, and epiglottis)	Nerve fibers (submucosa) Sensory corpuscular-like structures (Krause bulbs)	Human	[58]
	Oropharynx (nasal mucosa, soft palate, pharynx, epiglottis, and larynx)	Nerve fibers (subepithelial and intraepithelial) Epithelial cells Taste bud-like structures	Rats	[59]
	Tongue (taste papillae)	Nerve fibers (reached the outer epithelial layer in taste papillae)	Rats	[60]
	Oral cavity (tongue and hard palate)	Nerve fibers Cells in lamina propria End bulbs of Krause Epithelial cells	Human	[53]
	Oral and craniofacial structures (gingiva, incisal papilla, palatal ridge, lip, periodontal ligament)	Nerve fibers (subepithelial and intraepithelial, beneath and within taste buds) Taste bud cells	Rats	[61]

Table 2
Percentages of afferent neurons expressing TRP channels.

TRP channels	Ganglia, where the cell bodies of afferent neurons located	Innervating swallowing-related regions	Percentage of neurons expressing the channel	Species	Ref.
TRPV1	Jugular and petrosal	Pharynx	Around 33%	Rats	[44]
	Jugular and petrosal	Soft palate	Around 33%		
	Jugular	Trachea	59.3%	Rats	[50]
	Nodose		10.7%		
	Nodose	Laryngopharyngeal and associated laryngeal regions	23.3%	Rats	[37]
	Petrosal		52.3%		
	Jugular		50%		
	Jugular	Glossopharyngeal and vagus nerve-innervated regions	57.1%	Rats	[62]
	Petrosal		39.8%		
	Nodose		68.2%		
	Trigeminal	Tongue (anterior two-thirds)	17.9%	Rats	[64]
TRPV2	Jugular and petrosal	Pharynx	11.5%	Rats	[44]
	Jugular and petrosal	Soft palate	30.9%		
	Jugular	Trachea	8.8%	Rats	[50]
	Nodose		2.6%		
TRPV4	Nodose	SLN-innervated regions (laryngopharynx and associated laryngeal regions)	29.6%	Rats	[38]
	Petrosal		18.6%		
	Jugular		14.3%		
TRPA1	Nodose	SLN-innervated regions (laryngopharynx and associated laryngeal regions)	46.5%	Rats	[36]
	Petrosal		57%		
	Jugular		39.7%		
	Jugular	Glossopharyngeal and vagus nerves-innervated regions	26.9%	Rats	[62]
	Petrosal		30.3%		
	Nodose		29%		
TRPM8	Nodose	Laryngopharyngeal and associated laryngeal regions	46.8%	Rats	[37]
	Petrosal		50%		
	Jugular		46.3%		
	Jugular	Glossopharyngeal and vagus nerves-innervated regions	12.8%	Rats	[62]
	Petrosal		11.2%		
	Jugular	Pharynx	30.1%	Rats	[59]
	Petrosal		8.7%		

reduced the agonist-evoked swallowing reflexes, suggesting the involvement of a particular channel in swallowing reflex initiation [32,36–38,67,68].

Table 3
Pre-clinical studies evaluating the effects of TRP channel activation on initiation of swallowing reflexes.

TRP channels	Activators/ agonists of the channel	Regions where the activators applied	Concentration	Outcome	Species	Ref.
TRPV1	Capsaicin	Laryngopharynx and associated laryngeal regions	25 μM	1. The agonist triggered many swallowing reflexes 2. The number of agonist-induced reflexes was more than that of distilled water 3. The agonist shortened the swallowing interval compared to that of distilled water 4. A TRPV1 antagonist significantly reduced the number of agonist-induced swallowing reflexes and lengthened the swallowing intervals	Rats	[37]
	Capsaicin	Larynx	10 μM	The agonist triggered more swallowing reflexes than saline	Guinea pigs	[65]
	Capsaicin	Vocal folds	10 μM	The agonist triggered many swallowing reflexes	Rats	[66, 69]
	Capsaicin	Vocal folds	10 μM	1. The agonist triggered many swallowing reflexes 2. A TRPV1 antagonist significantly reduced the agonist-induced swallowing reflexes	Rats	[67, 68]
	Hydrochloric acid	Vocal folds	0.1 N	1. The agonist triggered many swallowing reflexes 2. A TRPV1 antagonist significantly reduced the agonist-induced swallowing reflexes	Rats	[67]
	Capsaicin	Pharyngolarynx	600 nM	The agonist overcomes the hampered ability to trigger swallowing reflexes in a dysphagia model	Rats (with transient occlusion of the middle cerebral artery)	[70]
	Capsaicin	Posterior tongue and vallecula	10 ppm (33 μM)	1. The agonist improved swallowing safety by decreasing the incidences of penetration and aspiration 2. The size of the boluses decreased after the agonist application	Infant pig (with a unilateral SLN lesion)	[71]
TRPV4	GSK1016790A	Laryngopharynx and associated laryngeal regions	1 μM to 500 μM	1. The agonist triggered swallowing reflexes in a dose-dependent manner 2. The number of agonist-induced reflexes was more than that of saline/vehicle for the agonist 3. A TRPV4 antagonist significantly reduced the number of agonist-induced swallowing reflexes and lengthened the swallowing intervals	Rats	[38]
TRPA1	Allyl isothiocyanate	Laryngopharynx and associated laryngeal regions	0.25–10 mM	1. The agonist triggered swallowing reflexes in a dose-dependent manner 2. The number of agonist-induced reflexes was more than that of saline 3. A TRPA1 antagonist significantly reduced the number of agonist-induced swallowing reflexes and lengthened the swallowing intervals	Rats	[36]
TRPM8	Menthol	Laryngopharynx and associated laryngeal regions	50 mM	1. The agonist triggered many swallowing reflexes 2. The number of agonist-induced reflexes was more than that of distilled water 3. The agonist shortened the swallowing interval compared to that of distilled water 4. A TRPM8 antagonist significantly reduced the number of agonist-induced swallowing reflexes and lengthened the swallowing intervals	Rats	[37]

4.2. TRP channel activation reduces the latency to swallow response onset or accelerates the timing of various swallowing events in patients with oropharyngeal dysphagia

Clinical studies, including randomized trials, have evaluated the effects of acute (Table 4) and repeated (Table 5) TRP channel activation on swallowing in patients with oropharyngeal dysphagia of various etiologies. In those studies, solutions containing low concentrations of TRP channel activators/agonists were applied to peripheral swallowing-related regions or mixed in foods or boluses for ingestion by participants/patients [72–85]. Some studies evaluated the effects of TRP channel activation on the latency to swallow response onset or various swallowing parameters [72,75–77,80,81,86]. Other studies used videofluoroscopy to evaluate various biomechanical events or parameters (e.g., laryngeal vestibule closing time, upper esophageal sphincter opening time, penetration into the larynx, presence of pharyngeal residue, and bolus propulsion velocity) during swallowing [73,77,78, 82–84]. These studies showed that both acute and repeated TRP channel activation reduce the latency to swallow response onset, increase the frequency of spontaneous swallowing, and accelerate the timing of various swallowing events (including closure of the laryngeal vestibule, opening of the upper esophageal sphincter, and movement of the hyoid bone and larynx). Both types of TRP channel activation also improved swallowing safety by reducing penetration of food particles into the airway. No serious adverse effects/complications were reported in those studies.

Some studies have evaluated the effects of acute or repeated inhalation of TRP channel activators on swallowing [88–90]. The inhalation of TRP channel activators reduced the latency to swallow response onset or improved swallowing performance. Additionally, the level of neuropeptide substance P in saliva increased upon daily inhalation of TRP channel activators or by daily ingestion of foods mixed with TRP channel activators for a specific period of time [74,88]. Substance P may play a facilitatory role in swallowing initiation. Some studies used an activator that can activate more than one TRP channel or a mixture of TRP channel activators to stimulate multiple TRP channels; the results showed swallowing performance improvements [78,82,83,88–90].

Table 4
Clinical studies evaluating the effects of acute TRP channel activation on the swallow response or various biomechanical swallowing events.

TRP channels	Activators/ agonists of the channel	Concentration	Mode of application of the activators	Participants/ Patients	Outcome	Ref
TRPV1	Capsaicin	1 nM to 1 μM	The solution of the activator applied to the pharyngeal region	Older patients with oropharyngeal dysphagia	Reduction of the time to initiate a swallow response	[72]
	Capsaicinoid	150 μM	The activator was mixed with nectar bolus and ingested by the patients	Older patients with oropharyngeal dysphagia	1. Reduction of the closing time for the laryngeal vestibule 2. Reduction of the opening time for the upper esophageal sphincter 3. Reduction of the maximal vertical movement time of the hyoid bone and larynx 4. Reduction of the occurrence of penetration to the larynx 5. Reduction of the presence of pharyngeal residue	[73]
	Capsaicinoid	150 μM	The activator was mixed with nectar bolus and ingested by the patients	Patients with oropharyngeal dysphagia due to stroke/ neurodegenerative diseases/ age	1. Reduction of the closing time for the laryngeal vestibule 2. Reduction of the occurrence of penetration to the larynx 3. Reduction of the presence of pharyngeal residue 4. Increase of the velocity for bolus propulsion	[78]
	Capsaicinoid	10 μM/50 μM	The solution of the activator ingested by the participants	Healthy participants without oropharyngeal dysphagia	1. Improvement in swallowing efficacy by increasing the strength of pharyngeal swallow and time for upper esophageal sphincter activation and relaxation 2. Increase of substance P level in saliva when 50 μM dose was used, and the increase of substance P level lasted for 15 min after application of the activator	[79]
	Capsiate	1–100 nM	The solution of the activator applied to the pharyngeal region	Patients with oropharyngeal dysphagia associated with a history of aspiration pneumonia	Reduction of the time to initiate a swallow response	[80]
	Capsaicin	10 μM	The solution of the activator ingested by the participants	Patients with oropharyngeal dysphagia due to stroke	Increase the frequency of spontaneous swallowing	[87]
	Capsaicin	0.5 g of 0.025%	The activator was mixed in an ointment and placed into the ear canal	Older patients with oropharyngeal dysphagia	Improve the swallowing function (swallowing function evaluated by an endoscopic swallowing scoring where a high score indicated impairment in swallowing function)	[86]
TRPM8	Menthol	100 μm to 10 mM	The solution of the activator applied to the pharyngeal region	Older patients with oropharyngeal dysphagia	Reduction of the time to initiate a swallow response	[81]
	Menthol	1 mM and 10 mM	The activator was mixed with nectar bolus and ingested by the patients.	Patients with oropharyngeal dysphagia due to stroke/ neurodegenerative diseases/ age	1. Reduction of the closing time for the laryngeal vestibule. 2. Reduction of the occurrence of penetration to the larynx	[78]
TRPA1	A mixture of cinnamaldehyde and zinc	Cinnamaldehyde (756.6 μM) + Zinc (70 μM)	The activators were mixed with nectar bolus and ingested by the patients	Patients with oropharyngeal dysphagia due to stroke/ neurodegenerative diseases/ age	1. Reduction of the closing time for the laryngeal vestibule 2. Reduction of the opening time for the upper esophageal sphincter 3. Reduction of the penetration-aspiration scale score 4. Increase the frequency of safe swallows 5. Reduction of the time to evoke a cortical response to pharyngeal electrical stimulation	[82]
	Citral	1.6 mM	The activator was mixed with nectar bolus and ingested by the patients	Patients with oropharyngeal dysphagia due to stroke/ neurodegenerative diseases/ age	1. Reduction of the closing time for the laryngeal vestibule 2. Reduction of the opening time for the upper esophageal sphincter	[82]
TRPV1 and TRPA1	Piperine	150 μM and 1 mM	The activator was mixed with nectar bolus and ingested by the patients	Patients with oropharyngeal dysphagia due to stroke/ neurodegenerative diseases/ age	1. Reduction of the closing time for the laryngeal vestibule 2. Reduction of the maximal anterior movement time of the hyoid bone 3. Reduction of the penetration-aspiration scale score 4. Reduction of the occurrence of penetration to the larynx	[83]

(*continued on next page*)

Table 4 (*continued*)

TRP channels	Activators/ agonists of the channel	Concentration	Mode of application of the activators	Participants/ Patients	Outcome	Ref
	Black pepper oil	100 μL for 1 min	The activator was applied to the nostrils with a paper stick for inhalation	Older patients with oropharyngeal dysphagia associated with cerebrovascular diseases	Distilled water-induced swallow response time was reduced	[88]
	Piperine	150 μM and 1 mM	The activator was mixed with nectar bolus and ingested by the patients	Patients with oropharyngeal dysphagia due to stroke/ neurodegenerative diseases/ age	1. Reduction of the closing time for the laryngeal vestibule 2. Reduction of the occurrence of penetration 3. The velocity of bolus propulsion increased	[78]
TRPV1, TRPA1 and TRPV3	Vanillin	7 L/min for 200 ms	The activator was delivered ortho-and retro-nasally	Healthy participants	The swallowing frequency to continuous intraoral glucose solution increased when the activator delivered retro-nasally	[89]
TRPA1 and TRPM8	Citral and isopulegol	Citral (1.6 mM) + Isopulegol (1.3 mM)	The activators were mixed with nectar bolus and ingested by the patients	Patients with oropharyngeal dysphagia due to stroke/ neurodegenerative diseases/ age	Reduction of the opening time for the upper esophageal sphincter	[82]

Table 5
Clinical studies evaluating the effects of repeated TRP channel activation on the swallow response or various biomechanical swallowing events.

TRP channels	Activators/ agonists of the channel	Concentration or dose	Mode of application of the activators	Participants/ Patients	Outcome	Ref
TRPV1	Capsaicinoid	10 μM	The activator was mixed with nectar bolus, and the patients ingested the bolus three times/day before meals for ten days	Older patients with oropharyngeal dysphagia	1. Reduction of the closing time for the laryngeal vestibule 2. Reduction of the penetration-aspiration scale score	[84]
	Capsaicin	1.5 μg/10 g of pickled cabbage	The activator was mixed with pickled cabbage, and the participants ingested the cabbage before meals for 20 days	Healthy participants without oropharyngeal dysphagia	Reduction of the time to initiate a swallow response	[85]
	Capsaicin	1.5 μg	The activator was mixed with lozenges, and the patients chewed the lozenge before meals for four weeks	Older patients with oropharyngeal dysphagia associated with cerebrovascular diseases	Reduction of the time to initiate a swallow response	[75]
	Capsaicin	0.75 μg	The activator was mixed with thin film foods, and the patients ingested the film food before meals for one week	Older patients with oropharyngeal dysphagia	1. Reduction of the duration of the cervical esophageal opening 2. Reduction of the symptoms of oropharyngeal dysphagia 3. Increase of concentration of the substance P in saliva in patients who showed improvement in swallowing	[74]
	Capsaicin	150 μM	The activator was mixed with nectar bolus, and the patients ingested the nectar bolus and received a cold thermal, tactile stimulation before meals for three weeks	Older patients with oropharyngeal dysphagia associated with a history of stroke	Improve the parameters of swallowing function assessed by swallowing assessment tools.	[76]
	Capsaicinoid	10 μM	The activator was mixed with nectar bolus, and the patients ingested the nectar bolus before meals for ten days	Older patients with oropharyngeal dysphagia	1. Reduction of the prevalence of aspiration. 2. Reduction of the score of the penetration-aspiration scale	[77]
TRPV1 and TRPA1	Black pepper oil	100 μL for 1 min	The activator was applied to the nostrils with a paper stick for inhalation three times/day before meals for 30 days	Older patients with oropharyngeal dysphagia associated with cerebrovascular diseases	1. Distilled water-induced swallow response time was reduced 2. Substance P level in serum increased	[88]
	Black pepper oil	100 μL for 1 min	The activator was applied to the nostrils with a paper stick for inhalation three times/day before meals for three months	Pediatric patients associated with severe neurological disorders often under tube feeding	1. The amount of oral intake of foods increased 2. Swallowing-related movements increased	[90]

4.3. TRP channel activation promotes neuroplasticity in swallowing-related networks in the brain

Clinical studies have investigated whether TRP channel activation in peripheral swallowing-related regions leads to neuronal plasticity development in cortical swallowing-related neuronal networks. In patients with oropharyngeal dysphagia, acute or repeated TRP channel activation increased the amplitude of a cortical response (pharyngeal event-related potentials assessed by electroencephalography) and reduced the latency to initiation of that response after pharyngeal electrical stimulation [82,84]. Repeated inhalation of TRP channel agonists increased regional blood flow in some cortical swallowing-related areas [88]. Additionally, TRP channel activation increased excitability in the swallowing-related motor cortex [91]. These findings indicate that TRP channel activation in peripheral swallowing-related regions may promote neuroplasticity development in swallowing-related neuronal networks..

Table 6
Evidence of cortical neuroplasticity development after TRP channel activation in peripheral swallowing-related regions.

TRP channels	Activators/ agonists of the channel	Concentration or dose	Mode of application of the activators	Participants/ Patients	Outcome	Ref
TRPV1	Capsaicinoid	10 μM	The activator was mixed with nectar bolus and the patients ingested the bolus three times/day before meals for ten days	Older patients with oropharyngeal dysphagia	1. Increase of the cortical sensorial response amplitude to pharyngeal electrical stimulation. 2. Reduction of the time to evoke a cortical sensorial response to pharyngeal electrical stimulation 3. Reduction of the time to evoke a cortical sensorial response to pharyngeal electrical stimulation was strongly correlated with the reductions in laryngeal vestibule closure time, indicating a relationship between enhanced cortical activity and improved swallowing function	[84]
	Capsaicin	10 μM	The solution of the activator ingested by the patients	Patients with oropharyngeal dysphagia due to stroke	Enhancement of motor cortex excitability	[91]
TRPA1	A mixture of cinnamaldehyde and zinc	Cinnamaldehyde (756.6 μM) + Zinc (70 μM)	The activators were mixed with nectar bolus and ingested by the patients.	Patients with oropharyngeal dysphagia due to stroke/ neurodegenerative diseases/ age	Reduction of the time to evoke a cortical response to pharyngeal electrical stimulation	[82]
TRPV1 and TRPA1	Black pepper oil	100 μL for 1 min	The activator was applied to the nostrils with a paper stick for inhalation three times/day before meals for 30 days	Aged patients with oropharyngeal dysphagia associated with cerebrovascular diseases	The blood flows in the right orbitofrontal and left insular cortex increased	[88]

5. Neurophysiological mechanisms of TRP channel activation-induced swallowing improvement

The basic pattern of swallowing is generated by a brainstem neural network known as the central pattern generator for swallowing (sCPG) (Fig. 1) [8,92,93]. It consists of dorsal and ventral neuronal groups. The dorsal neuronal group is located within the nucleus of the solitary tract (NTS) and the adjacent reticular formations. It is involved in generating the swallowing pattern, shaping, and timing of sequential or rhythmic swallowing. The ventral neuronal group located adjacent to the nucleus ambiguous distributes the swallowing drive to the motor neurons of several cranial nerves {e.g., trigeminal (V), facial (VII), glossopharyngeal (IX), vagus (X), hypoglossal (XII)}. The sCPG is activated by commands from the cerebral cortex and sensory inputs from peripheral swallowing-related regions. The sensory nerve fibers of several cranial nerves carry the peripheral sensory inputs (Fig. 1). TRP channel activation in peripheral swallowing-related regions excites sensory nerves, thereby increasing peripheral sensory inputs to the brainstem sCPG, as well as the cortical and subcortical swallowing-related regions; this process facilitates swallowing [32,34]. The activation of channels present in the sensory nerves causes cations (e.g., Ca^{2+}) to enter the nerves, resulting in nerve excitation (Fig. 1) [32]. TRP channel-expressing epithelial cells may also indirectly excite the nerves [32,34]. Epithelial cells may release neuroactive molecules (e.g., adenosine triphosphate [ATP]) upon exposure to TRP channel agonists, thereby exciting intra-epithelial or subepithelial nerves [32]. Several studies have shown that epithelial cells release ATP in response to TRP channel agonists [94–97]. Neuroactive molecules may also be released into saliva in response to TRP channel agonists. The levels of neuropeptide substance P in saliva increased upon TRP channel activation in healthy individuals [79] and patients with oropharyngeal dysphagia [74,88]. Sensory nerves can also release neuropeptides (e.g., substance P or calcitonin gene-related peptide) upon excitation by TRP channel agonists. Increased levels of neuroactive molecules in peripheral swallowing-related regions may further enhance the excitation of swallowing-related sensory nerves [32]. An increase in sensory nerve excitation may cause an increase in motor drive from the sCPG and cortical swallowing-related motor areas, thereby promoting swallowing [32,34].

Additionally, TRP channel activation in peripheral swallowing-related regions may cause prolonged excitatory neurotransmitter release in the NTS [32]. *In vitro* activation of TRPV1 in solitary tract afferent nerves reportedly causes prolonged glutamate release in the NTS [98–100]; this prolonged release may facilitate swallowing initiation [32]. This hypothesis is supported by animal studies in which repeated swallowing reflexes were initiated upon TRP channel activation in peripheral swallowing-related regions [36–38].

Furthermore, repeated TRP channel activation in peripheral swallowing-related regions may induce plasticity in cortical and subcortical swallowing-related neuronal networks, thereby promoting swallowing [32,34]. In patients with oropharyngeal dysphagia, repeated TRP channel activation in peripheral swallowing-related regions may facilitate the conduction and integration of peripheral sensory inputs in cortical swallowing-related neuronal networks [82,84].

6. Advantages of TRP channel targeting in the treatment of oropharyngeal dysphagia

The pharmacological targeting of TRP channels for treatment of oropharyngeal dysphagia has several advantages relative to conventional compensatory treatment strategies. The addition of thickeners, a widely used compensatory treatment strategy to increase the viscosity of the bolus to be swallowed, improves swallowing safety by reducing bolus velocity in the pharynx [23,101]. Higher viscosities can also delays laryngeal vestibular closure, and upper esophageal opening, thereby slowing the swallowing response [101–103]. Although the use of thickeners to increase bolus viscosity improves swallowing safety, it can increase the prevalence of bolus residue in oropharyngeal regions [23]. Additionally, thickeners are poorly tolerated by patients, resulting in low treatment adherence [23,104,105]. In contrast, TRP channel activation in peripheral swallowing-related regions improves swallowing safety by accelerating the swallowing response, laryngeal vestibular closure, and upper esophageal opening, thereby promoting the restoration of impaired swallowing physiology [32,34,82,84,103]. It also improves swallowing efficacy and reduces the prevalence of bolus residue in oropharyngeal regions [32,34,82,84,103]. Natural TRP agonists are inexpensive and can easily be added to food for patients with presbyphagia (i.e., age-related changes in the swallowing mechanism) or patients with dysphagia who have not discontinued oral intake [79].

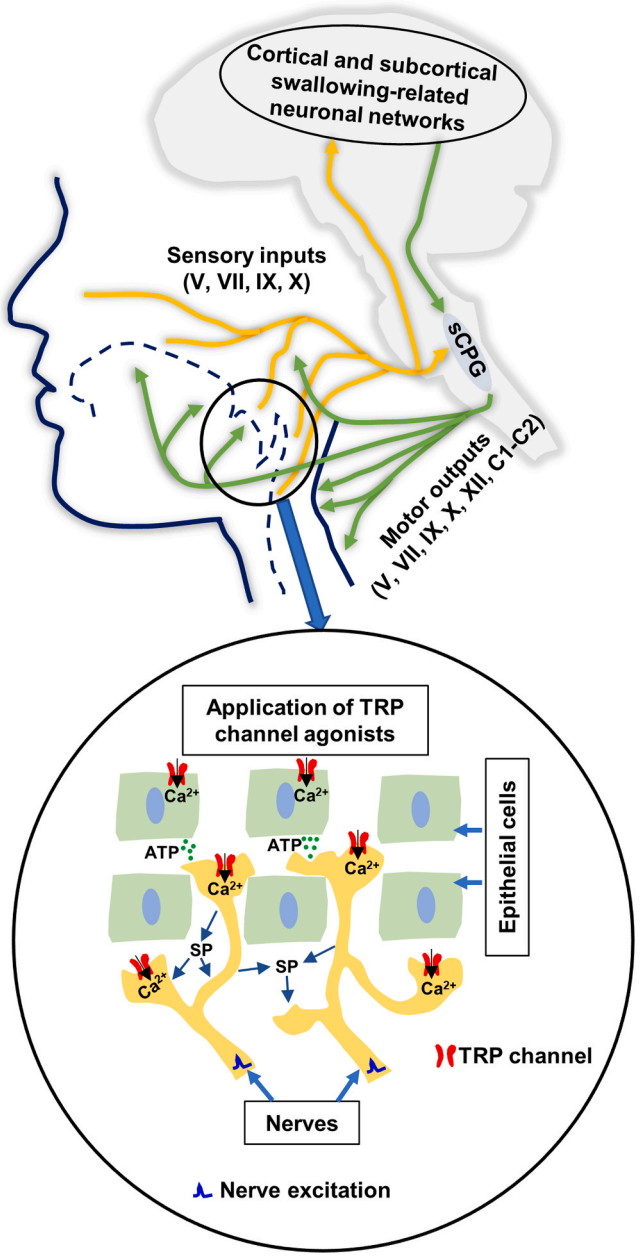

Fig. 1. Possible neurophysiological and molecular mechanisms underlying improvements in swallowing function through TRP channel activation. The application of TRP channel agonists in peripheral swallowing-related regions activates TRP channels expressed in epithelial cells and nerve fibers, causing cation entry (e.g., Ca2 +) into these structures. Upon activation, epithelial cells may release neuroactive substances (e.g., ATP), which can excite nearby intraepithelial and subepithelial nerve fibers. Excited afferent nerves may release neuropeptides (e.g., SP) that cause further nerve excitation. Increased nerve excitation causes increased sensory inputs to travel through the sensory branches of several cranial nerves (V, VII, IX, X) to the sCPG, as well as the cortical and subcortical swallowing-related regions of the brain. After integration into the swallowing-related neuronal networks of the brain and sCPG, the increased sensory inputs may increase motor output to peripheral swallowing-related muscles, which travels through the motor branches of several cranial nerves (V, VII, IX, X, XII, and C1–C2), thereby improving swallowing performance. V: trigeminal nerve; VII: facial nerve; IX: glossopharyngeal nerve; X: vagus nerve; XII; hypoglossal nerve, C1–C2: cervical nerves 1–2; ATP: adenosine triphosphate; sCPG: central pattern generator for swallowing; Ca^{2+}: calcium ions; SP: substance P.

The addition of natural TRP channel agonists to foods may also increase tolerability and patient compliance [106]. Therefore, TRP channel agonists can be used in the development of foods for patients with oropharyngeal dysphagia. In this context, a recent review paper has highlighted the importance of TRP channel agonists in the formulation of swallow-safe food [106].

7. Conclusion

The results of various studies have suggested that TRP channel targeting in peripheral swallowing-related regions is a promising pharmacological treatment strategy for oropharyngeal dysphagia. Both acute and intermediate-term repeated administration of TRP channel agonists improved swallowing safety and physiology in patients with oropharyngeal dysphagia [32,34,103]. Although the repeated administration of TRP channel agonists was well-tolerated by patients [32,34,35,103], the effects of long-term administration have not been studied. In the future, long-term multicenter clinical trials involving large numbers of patients with oropharyngeal dysphagia are needed to understand the effects of long-term administration of TRP channel agonists. Additional basic research is necessary to understand the molecular and neurophysiological mechanisms by which TRP channel agonists facilitate improved swallowing performance. A detailed understanding of the swallowing-related mechanisms and functions of various TRP channels may lead to the development of effective therapeutics for oropharyngeal dysphagia.

Scientific field of dental science

Oral physiology.

Funding

This work was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI, Grant Numbers 17K11656 to JK and 20K09898 to MH. The grant-providing society had no role in the study design, collection, analysis, or interpretation of data.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Clavé P, Rofes L, Arreola V, Almirall J, Cabré M, Campins L, et al. Diagnosis and management of oropharyngeal dysphagia and its nutritional and respiratory complications in the elderly. Gastroenterol Res Pr 2011;2011:13. https://doi.org/10.1155/2011/818979.
[2] Daniels S. Neurological disorders affecting oral, pharyngeal swallowing. GI Motil Online 2006:2210. https://doi.org/https://www.nature.com/gimo/contents/pt1/full/gimo34.html.
[3] Oliveira AR de S, Costa AG de S, Morais HCC, Cavalcante TF, Lopes MV de O, de Araujo TL. Clinical factors predicting risk for aspiration and respiratory aspiration among patients with Stroke. Rev Lat Am Enferm 2015;23:216–24. https://doi.org/10.1590/0104-1169.0197.2545.
[4] Wirth R, Dziewas R, Beck AM, Clavé P, Hamdy S, Heppner HJ, et al. Oropharyngeal dysphagia in older persons – from pathophysiology to adequate intervention: a review and summary of an international expert meeting. Clin Inter Aging 2016;11:189–208. https://doi.org/10.2147/CIA.S97481.
[5] Ortega O, Cabre M, Clave P. Oropharyngeal dysphagia: aetiology and effects of ageing. J Gastroenterol Hepatol Res 2014;3:1049–54. https://doi.org/10.6051/j.issn.2224-3992.2014.03.408-4.
[6] Robbins J, Bridges AD, Taylor A. Oral, pharyngeal and esophageal motor function in aging. GI Motil Online 2006:1–21. https://doi.org/10.1038/gimo39.
[7] Espinosa-Val C, Martín-Martínez A, Graupera M, Arias O, Elvira A, Cabré M, et al. Prevalence, risk factors, and complications of oropharyngeal dysphagia in older patients with dementia. Nutrients 2020;12:863. https://doi.org/10.3390/nu12030863.
[8] Clavé P, Shaker R. Dysphagia: current reality and scope of the problem. Nat Rev Gastroenterol Hepatol 2015;12:259–70. https://doi.org/10.1038/nrgastro.2015.49.

[9] Matsuo K, Palmer JB. Anatomy and physiology of feeding and swallowing: normal and abnormal. Phys Med Rehabil Clin N Am 2008;19:691–707. https://doi.org/10.1016/j.pmr.2008.06.001.
[10] Tagliaferri S, Lauretani F, Pelá G, Meschi T, Maggio M. The risk of dysphagia is associated with malnutrition and poor functional outcomes in a large population of outpatient older individuals. Clin Nutr 2019;38:2684–9. https://doi.org/10.1016/j.clnu.2018.11.022.
[11] de Sire A, Ferrillo M, Lippi L, Agostini F, de Sire R, Ferrara PE, et al. Sarcopenic dysphagia, malnutrition, and oral frailty in elderly: a comprehensive review. Nutrients 2022;14:982. https://doi.org/10.3390/nu14050982.
[12] Carrión S, Cabré M, Monteis R, Roca M, Palomera E, Serra-Prat M, et al. Oropharyngeal dysphagia is a prevalent risk factor for malnutrition in a cohort of older patients admitted with an acute disease to a general hospital. Clin Nutr 2015;34:436–42. https://doi.org/10.1016/j.clnu.2014.04.014.
[13] Cabre M, Serra-Prat M, Palomera E, Almirall J, Pallares R, Clavé P. Prevalence and prognostic implications of dysphagia in elderly patients with pneumonia. Age Ageing 2009;39:39–45. https://doi.org/10.1093/ageing/afp100.
[14] Ebihara S, Sekiya H, Miyagi M, Ebihara T, Okazaki T. Dysphagia, dystussia, and aspiration pneumonia in elderly people. J Thorac Dis 2016;8:632–9. https://doi.org/10.21037/jtd.2016.02.60.
[15] Cabré M, Serra-Prat M, Force L, Almirall J, Palomera E, Clavé P. Oropharyngeal dysphagia is a risk factor for readmission for pneumonia in the very elderly persons: observational prospective study. A:330–7 J Gerontol - Ser A Biol Sci Med Sci 2014;69. https://doi.org/10.1093/gerona/glt099.
[16] Koidou I, Kollias N, Sdravou K, Grouios G. Dysphagia: a short review of the current state. Educ Gerontol 2013;39:812–27. https://doi.org/10.1080/03601277.2013.766518.
[17] Seaman WB. Pharyngeal and upper esophageal dysphagia. JAMA J Am Med Assoc 1976;235:2643–6. https://doi.org/10.1001/jama.1976.03260500051035.
[18] Spieker MR. Evaluating dysphagia. Am Fam Physician 2000;61:3639–48.
[19] Jaffer NM, Ng E, Au FWF, Steele CM. Fluoroscopic evaluation of oropharyngeal dysphagia: Anatomic, technical, and common etiologic factors. Am J Roentgenol 2015;204:49–58. https://doi.org/10.2214/AJR.13.12374.
[20] Rofes L, Arreola V, Romea M, Palomera E, Almirall J, Cabré M, et al. Pathophysiology of oropharyngeal dysphagia in the frail elderly. Neurogastroenterol Motil 2010;22:851–e230. https://doi.org/10.1111/j.1365-2982.2010.01521.x.
[21] Clavé P, De Kraa M, Arreola V, Girvent M, Farré R, Palomera E, et al. The effect of bolus viscosity on swallowing function in neurogenic dysphagia. Aliment Pharm Ther 2006;24:1385–94. https://doi.org/10.1111/j.1365-2036.2006.03118.x.
[22] Vilardell N, Rofes L, Arreola V, Martin A, Muriana D, Palomeras E, et al. Videofluoroscopic assessment of the pathophysiology of chronic poststroke oropharyngeal dysphagia. Neurogastroenterol Motil 2017;29:1–8. https://doi.org/10.1111/nmo.13111.
[23] Newman R, Vilardell N, Clavé P, Speyer R. Effect of bolus viscosity on the safety and efficacy of swallowing and the kinematics of the swallow response in patients with oropharyngeal dysphagia: white paper by the european society for swallowing disorders (ESSD). Dysphagia 2016;31:232–49. https://doi.org/10.1007/s00455-016-9696-8.
[24] Cook IJ. Oropharyngeal dysphagia. Gastroenterol Clin North Am 2009;38:411–31. https://doi.org/10.1016/j.gtc.2009.06.003.
[25] Bulat RS, Orlando RC. Oropharyngeal dysphagia. Curr Treat Options Gastroenterol 2005;8:269–74. https://doi.org/10.1007/s11938-005-0019-7.
[26] Cabib C, Ortega O, Kumru H, Palomeras E, Vilardell N, Alvarez-Berdugo D, et al. Neurorehabilitation strategies for poststroke oropharyngeal dysphagia: from compensation to the recovery of swallowing function. Ann N Y Acad Sci 2016;1380:121–38. https://doi.org/10.1111/nyas.13135.
[27] Ortega O, Martín A, Clavé P. Diagnosis and management of oropharyngeal dysphagia among older persons, state of the art. J Am Med Dir Assoc 2017;18:576–82. https://doi.org/10.1016/j.jamda.2017.02.015.
[28] Martino R, McCulloch T. Therapeutic intervention in oropharyngeal dysphagia. Nat Rev Gastroenterol Hepatol 2016;13:665–79. https://doi.org/10.1038/nrgastro.2016.127.
[29] Langmore SE, Pisegna JM. Efficacy of exercises to rehabilitate dysphagia: a critique of the literature. Int J Speech Lang Pathol 2015;17:222–9. https://doi.org/10.3109/17549507.2015.1024171.
[30] Speyer R, Baijens L, Heijnen M, Zwijnenberg I. Effects of therapy in oropharyngeal dysphagia by speech and language therapists: a systematic review. Dysphagia 2010;25:40–65. https://doi.org/10.1007/s00455-009-9239-7.
[31] Wirth R, Dziewas R. Dysphagia and pharmacotherapy in older adults. Curr Opin Clin Nutr Metab Care 2019;22:25–9. https://doi.org/10.1097/MCO.0000000000000523.
[32] Hossain MZ, Ando H, Unno S, Kitagawa J. Targeting chemosensory ion channels in peripheral swallowing-related regions for the management of oropharyngeal dysphagia. Int J Mol Sci 2020;21:1–45. https://doi.org/10.3390/ijms21176214.
[33] Cheng I, Sasegbon A, Hamdy S. Effects of pharmacological agents for neurogenic oropharyngeal dysphagia: a systematic review and meta-analysis. Neurogastroenterol Motil 2022;34:e14220. https://doi.org/10.1111/nmo.14220.
[34] Clavé P, Ortega O, Rofes L, Alvarez-Berdugo D, Tomsen N. Brain and pharyngeal responses associated with pharmacological treatments for oropharyngeal dysphagia in older patients. Dysphagia 2023:1–18. https://doi.org/10.1007/s00455-023-10578-x.
[35] Jiang W, Zou Y, Huang L, Zeng Y, Xiao LD, Chen Q, et al. Gustatory stimulus interventions for older adults with dysphagia: a scoping review. Aging Clin Exp Res 2023:1–14. https://doi.org/10.1007/s40520-023-02437-4.
[36] Hossain MZ, Ando H, Unno S, Kitagawa J. TRPA1s act as chemosensors but not as cold sensors or mechanosensors to trigger the swallowing reflex in rats. Sci Rep 2022;12:3431. https://doi.org/10.1038/s41598-022-07400-3.
[37] Hossain MZ, Ando H, Unno S, Masuda Y, Kitagawa J. Activation of TRPV1 and TRPM8 channels in the larynx and associated laryngopharyngeal regions facilitates the swallowing reflex. Int J Mol Sci 2018;19:4113. https://doi.org/10.3390/ijms19124113.
[38] Hossain MZ, Ando H, Unno S, Roy RR, Kitagawa J. Pharmacological activation of transient receptor potential vanilloid 4 promotes triggering of the swallowing reflex in rats. Front Cell Neurosci 2023;17:65. https://doi.org/10.3389/fncel.2023.1149793.
[39] Nilius B, Szallasi A. Transient receptor potential channels as drug targets: from the science of basic research to the art of medicine. Pharm Rev 2014;66:676–814. https://doi.org/10.1124/pr.113.008268.
[40] Clapham DE. TRP channels as cellular sensors. Nature 2003;426:517–24. https://doi.org/10.1038/nature02196.
[41] Hossain MZ, Bakri MM, Yahya F, Ando H, Unno S, Kitagawa J. The role of transient receptor potential (TRP) channels in the transduction of dental pain. Int J Mol Sci 2019;20:526. https://doi.org/10.3390/ijms20030526.
[42] Nilius B. TRP channels in disease. Biochim Biophys Acta - Mol Basis Dis 2007;1772:805–12. https://doi.org/10.1016/j.bbadis.2007.02.002.
[43] Alvarez-Berdugo D, Rofes L, Farré R, Casamitjana JF, Enrique A, Chamizo J, et al. Localization and expression of TRPV1 and TRPA1 in the human oropharynx and larynx. Neurogastroenterol Motil 2016;28:91–100. https://doi.org/10.1111/nmo.12701.
[44] Sasaki R, Sato T, Yajima T, Kano M, Suzuki T, Ichikawa H. The distribution of TRPV1 and TRPV2 in the rat pharynx. Cell Mol Neurobiol 2013;33:707–14. https://doi.org/10.1007/s10571-013-9938-3.
[45] Hamamoto T, Takumida M, Hirakawa K, Tatsukawa T, Ishibashi T. Localization of transient receptor potential vanilloid (TRPV) in the human larynx. Acta Otolaryngol 2009;129:560–8. https://doi.org/10.1080/00016480802273108.
[46] Hamamoto T, Takumida M, Hirakawa K, Takeno S, Tatsukawa T. Localization of transient receptor potential channel vanilloid subfamilies in the mouse larynx. Acta Otolaryngol 2008;128:685–93. https://doi.org/10.1080/00016480701669489.
[47] Koike S, Uno T, Bamba H, Shibata T, Okano H, Hisa Y. Distribution of vanilloid receptors in the rat laryngeal innervation. Acta Otolaryngol 2004;124:515–9. https://doi.org/10.1080/00016480310000674.
[48] Yamamoto Y, Taniguchi K. Immunolocalization of VR1 and VRL1 in rat larynx. Auton Neurosci Basic Clin 2005;117:62–5. https://doi.org/10.1016/j.autneu.2004.11.003.
[49] Seki N, Shirasaki H, Kikuchi M, Sakamoto T, Watanabe N, Himi T. Expression and localization of TRPV1 in human nasal mucosa. Rhinology 2006;44:128–34.
[50] Yamamoto Y, Sato Y, Taniguchi K. Distribution of TRPV1- and TRPV2-immunoreactive afferent nerve endings in rat trachea. J Anat 2007;211:775–83. https://doi.org/10.1111/j.1469-7580.2007.00821.x.
[51] Kido MA, Muroya H, Yamaza T, Terada Y, Tanaka T. Vanilloid receptor expression in the rat tongue and palate. J Dent Res 2003;82:393–7. https://doi.org/10.1177/154405910308200513.
[52] Ishida Y, Ugawa S, Ueda T, Murakami S, Shimada S. Vanilloid receptor subtype-1 (VR1) is specifically localized to taste papillae. Mol Brain Res 2002;107:17–22. https://doi.org/10.1016/S0169-328X(02)00441-2.
[53] Moayedi Y, Michlig S, Park M, Koch A, Lumpkin EA. Localization of TRP channels in healthy oral mucosa from human donors. ENEURO.0328-21.2022 Eneuro 2022;9. https://doi.org/10.1523/ENEURO.0328-21.2022.
[54] Uno T, Koike S, Hirota R, Bamba H, Hisa Y. Capsaicin receptor expression in rat laryngeal innervation. Ann Otol Rhinol Laryngol 2004;113:356–8. https://doi.org/10.1177/000348940411300503.
[55] Foote AG, Tibbetts J, Bartley SM, Thibeault SL. Localization of TRPV3/4 and PIEZO1/2 sensory receptors in murine and human larynges. Laryngoscope Invest Otolaryngol 2022;7:1963–72. https://doi.org/10.1002/lio2.968.
[56] De Carlos F, Cobo J, Macías E, Feito J, Cobo T, Calavia MG, et al. The sensory innervation of the human pharynx: searching for mechanoreceptors. Anat Rec 2013;296:1735–46. https://doi.org/10.1002/ar.22792.
[57] Matsumoto K, Ohishi A, Iwatsuki K, Yamazaki K, Takayanagi S, Tsuji M, et al. Transient receptor potential vanilloid 4 mediates sour taste sensing via type III taste cell differentiation. Sci Rep 2019;9:6686. https://doi.org/10.1038/s41598-019-43254-y.
[58] Alvarez-Berdugo D, Rofes L, Casamitjana JF, Enrique A, Chamizo J, Viña C, et al. TRPM8, ASIC1, and ASIC3 localization and expression in the human oropharynx. Neurogastroenterol Motil 2018;30:e13398. https://doi.org/10.1111/nmo.13398.
[59] Sato T, Fujita M, Kano M, Hosokawa H, Kondo T, Suzuki T, et al. The distribution of transient receptor potential melastatin-8 in the rat soft palate, epiglottis, and pharynx. Cell Mol Neurobiol 2013;33:161–5. https://doi.org/10.1007/s10571-012-9888-1.
[60] Abe J, Hosokawa H, Okazawa M, Kandachi M, Sawada Y, Yamanaka K, et al. TRPM8 protein localization in trigeminal ganglion and taste papillae. Mol Brain Res 2005;136:91–8. https://doi.org/10.1016/j.molbrainres.2005.01.013.
[61] Yajima T, Sato T, Hosokawa H, Kondo T, Saito M, Shimauchi H, et al. Distribution of transient receptor potential melastatin-8-containing nerve fibers in rat oral and craniofacial structures. Ann Anat 2015;201:1–5. https://doi.org/10.1016/j.aanat.2015.04.003.
[62] Hondoh A, Ishida Y, Ugawa S, Ueda T, Shibata Y, Yamada T, et al. Distinct expression of cold receptors (TRPM8 and TRPA1) in the rat nodose-petrosal ganglion complex. Brain Res 2010;1319:60–9. https://doi.org/10.1016/j.brainres.2010.01.016.

[63] Zhang L, Jones S, Brody K, Costa M, Brookes SJH. Thermosensitive transient receptor potential channels in vagal afferent neurons of the mouse. Am J Physiol - Gastrointest Liver Physiol 2004;286. https://doi.org/10.1152/ajpgi.00441.2003.
[64] Kanazawa T, Matsumoto S. Expression of transient receptor potential vanilloid 1 and anoctamin 1 in rat trigeminal ganglion neurons innervating the tongue. Brain Res Bull 2014;106:17–20. https://doi.org/10.1016/j.brainresbull.2014.04.015.
[65] Tsujimura T, Udemgba C, Inoue M, Canning BJ. Laryngeal and tracheal afferent nerve stimulation evokes swallowing in anaesthetized guinea pigs. J Physiol 2013;591:4667–79. https://doi.org/10.1113/jphysiol.2013.256024.
[66] Tsujimura T, Sakai S, Suzuki T, Ujihara I, Tsuji K, Magara J, et al. Central inhibition of initiation of swallowing by systemic administration of diazepam and baclofen in anaesthetized rats. Am J Physiol - Gastrointest Liver Physiol 2017; 312:G498–507. https://doi.org/10.1152/ajpgi.00299.2016.
[67] Yoshihara M, Tsujimura T, Suzuki T, Nagoya K, Shiraishi N, Magara J, et al. Sustained laryngeal transient receptor potential vanilloid 1 activation inhibits mechanically induced swallowing in anesthetized rats. Am J Physiol - Gastrointest Liver Physiol 2020;319:G412–9. https://doi.org/10.1152/AJPGI.00082.2020.
[68] Tsujimura T, Ueha R, Yoshihara M, Takei E, Nagoya K, Shiraishi N, et al. Involvement of the epithelial sodium channel in initiation of mechanically evoked swallows in anaesthetized rats. J Physiol 2019;597:2949–63. https://doi.org/10.1113/JP277895.
[69] Tsuji K, Tsujimura T, Sakai S, Suzuki T, Yoshihara M, Nagoya K, et al. Involvement of capsaicin-sensitive nerves in the initiation of swallowing evoked by carbonated water in anesthetized rats. Am J Physiol - Gastrointest Liver Physiol 2020;319:G564–72. https://doi.org/10.1152/AJPGI.00233.2020.
[70] Sugiyama N, Nishiyama E, Nishikawa Y, Sasamura T, Nakade S, Okawa K, et al. A novel animal model of dysphagia following stroke. Dysphagia 2014;29:61–7. https://doi.org/10.1007/s00455-013-9481-x.
[71] Edmonds CE, German RZ, Bond LE, Mayerl CJ. Oropharyngeal capsaicin exposure improves infant feeding performance in an animal model of superior laryngeal nerve damage. J Neurophysiol 2022;128:339–49. https://doi.org/10.1152/jn.00063.2022.
[72] Ebihara T, Sekizawa K, Nakazawa H, Sasaki H. Capsaicin and swallowing reflex. Lancet 1993;341:432. https://doi.org/10.1016/0140-6736(93)93023-T.
[73] Rofes L, Arreola V, Martin A, Clavé P. Natural capsaicinoids improve swallow response in older patients with oropharyngeal dysphagia. Gut 2013;62:1280–7. https://doi.org/10.1136/gutjnl-2011-300753.
[74] Nakato R, Manabe N, Shimizu S, Hanayama K, Shiotani A, Hata J, et al. Effects of capsaicin on older patients with oropharyngeal dysphagia: a double-blind, placebo-controlled, crossover study. Digestion 2017;95:210–20. https://doi.org/10.1159/000463382.
[75] Ebihara T, Takahashi H, Ebihara S, Okazaki T, Sasaki T, Watando A, et al. Capsaicin troche for swallowing dysfunction in older people. J Am Geriatr Soc 2005;53:824–8. https://doi.org/10.1111/j.1532-5415.2005.53261.x.
[76] Wang Z, Wu L, Fang Q, Shen M, Zhang L, Liu X. Effects of capsaicin on swallowing function in stroke patients with dysphagia: A randomized controlled trial. J Stroke Cereb Dis 2019;28:1744–51. https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.02.008.
[77] Ortega O, Rofes L, Martin A, Arreola V, López I, Clavé P. A comparative study between two sensory stimulation strategies after two weeks treatment on older patients with oropharyngeal dysphagia. Dysphagia 2016;31:706–16. https://doi.org/10.1007/s00455-016-9736-4.
[78] Alvarez-Berdugo D, Rofes L, Arreola V, Martin A, Molina L, Clavé P. A comparative study on the therapeutic effect of TRPV1, TRPA1, and TRPM8 agonists on swallowing dysfunction associated with aging and neurological diseases. Neurogastroenterol Motil 2018;30:e13185. https://doi.org/10.1111/nmo.13185.
[79] Suntrup-Krueger S, Muhle P, Kampe I, Egidi P, Ruck T, Lenze F, et al. Effect of capsaicinoids on neurophysiological, biochemical, and mechanical parameters of swallowing function. Neurotherapeutics 2021;18:1360–70. https://doi.org/10.1007/s13311-020-00996-2.
[80] Yamasaki M, Ebihara S, Ebihara T, Yamanda S, Arai H, Kohzuki M. Effects of capsiate on the triggering of the swallowing reflex in elderly patients with aspiration pneumonia. Geriatr Gerontol Int 2010;10:107–9. https://doi.org/10.1111/j.1447-0594.2009.00566.x.
[81] Ebihara T, Ebihara S, Watando A, Okazaki T, Asada M, Ohrui T, et al. Effects of menthol on the triggering of the swallowing reflex in elderly patients with dysphagia. Br J Clin Pharm 2006;62:369–71. https://doi.org/10.1111/j.1365-2125.2006.02666.x.
[82] Tomsen N, Alvarez-Berdugo D, Rofes L, Ortega O, Arreola V, Nascimento W, et al. A randomized clinical trial on the acute therapeutic effect of TRPA1 and TRPM8 agonists in patients with oropharyngeal dysphagia. Neurogastroenterol Motil 2020;32:e13821. https://doi.org/10.1111/nmo.13821.
[83] Rofes L, Arreola V, Martin A, Clavé P. Effect of oral piperine on the swallow response of patients with oropharyngeal dysphagia. J Gastroenterol 2014;49: 1517–23. https://doi.org/10.1007/s00535-013-0920-0.
[84] Tomsen N, Ortega O, Rofes L, Arreola V, Martin A, Mundet L, et al. Acute and subacute effects of oropharyngeal sensory stimulation with TRPV1 agonists in older patients with oropharyngeal dysphagia: a biomechanical and neurophysiological randomized pilot study. Ther Adv Gastroenterol 2019;12: 1756284819842043. https://doi.org/10.1177/1756284819842043.
[85] Shin S, Shutoh N, Tonai M, Ogata N. The effect of capsaicin-containing food on the swallowing response. Dysphagia 2016;31:146–53. https://doi.org/10.1007/s00455-015-9668-4.
[86] Kondo E, Jinnouchi O, Ohnishi H, Kawata I, Nakano S, Goda M, et al. Effects of aural stimulation with capsaicin ointment on swallowing function in elderly patients with non-obstructive dysphagia. Clin Inter Aging 2014;9:1661–7. https://doi.org/10.2147/CIA.S67602.
[87] Nascimento W, Tomsen N, Acedo S, Campos-Alcantara C, Cabib C, Alvarez-Larruy M, et al. Effect of aging, gender and sensory stimulation of trpv1 receptors with capsaicin on spontaneous swallowing frequency in patients with oropharyngeal dysphagia: a proof-of-concept study. Diagnostics 2021;11:461. https://doi.org/10.3390/diagnostics11030461.
[88] Ebihara T, Ebihara S, Maruyama M, Kobayashi M, Itou A, Arai H, et al. A randomized trial of olfactory stimulation using black pepper oil in older people with swallowing dysfunction. J Am Geriatr Soc 2006;54:1401–6. https://doi.org/10.1111/j.1532-5415.2006.00840.x.
[89] Welge-Lüssen A, Ebnöther M, Wolfensberger M, Hummel T. Swallowing is differentially influenced by retronasal compared with orthonasal stimulation in combination with gustatory stimuli. Chem Senses 2009;34:499–502. https://doi.org/10.1093/chemse/bjp024.
[90] Munakata M, Kobayashi K, Niisato-Nezu J, Tanaka S, Kakisaka Y, Ebihara T, et al. Olfactory stimulation using black pepper oil facilitates oral feeding in pediatric patients receiving long-term enteral nutrition. Tohoku J Exp Med 2008;214: 327–32. https://doi.org/10.1620/tjem.214.327.
[91] Cabib C, Nascimento W, Rofes L, Arreola V, Tomsen N, Mundet L, et al. Short-term neurophysiological effects of sensory pathway neurorehabilitation strategies on chronic poststroke oropharyngeal dysphagia. Neurogastroenterol Motil 2020; 32:e13887. https://doi.org/10.1111/nmo.13887.
[92] Yamamura K, Kitagawa J, Kurose M, Sugino S, Takatsuji H, Md Mostafeezur R, et al. Neural mechanisms of swallowing and effects of taste and other stimuli on swallow initiation. Biol Pharm Bull 2010;33:1786–90. https://doi.org/10.1248/bpb.33.1786.
[93] Jean A. Brain stem control of swallowing: neuronal network and cellular mechanisms. Physiol Rev 2001;81:929–69. https://doi.org/10.1152/physrev.2001.81.2.929.
[94] Wu L, Oshima T, Shan J, Sei H, Tomita T, Ohda Y, et al. PAR-2 activation enhances weak acid-induced ATP release through TRPV1 and ASIC sensitization in human esophageal epithelial cells. Am J Physiol - Gastrointest Liver Physiol 2015;309:G695–702. https://doi.org/10.1152/ajpgi.00162.2015.
[95] Ma J, Altomare A, Rieder F, Behar J, Biancani P, Harnett KM. ATP: A mediator for HCL-induced TRPV1 activation in esophageal mucosa. Am J Physiol - Gastrointest Liver Physiol 2011;301. https://doi.org/10.1152/ajpgi.00336.2011.
[96] Mihara H, Boudaka A, Sugiyama T, Moriyama Y, Tominaga M. Transient receptor potential vanilloid 4 (TRPV4)-dependent calcium influx and ATP release in mouse oesophageal keratinocytes. J Physiol 2011;589:3471–82. https://doi.org/10.1113/jphysiol.2011.207829.
[97] Mihara H, Suzuki N, Boudaka AA, Muhammad JS, Tominaga M, Tabuchi Y, et al. Transient receptor potential vanilloid 4-dependent calcium influx and ATP release in mouse and rat gastric epithelia. World J Gastroenterol 2016;22:5512–9. https://doi.org/10.3748/wjg.v22.i24.5512.
[98] Peters JH, McDougall SJ, Fawley JA, Andresen MC. TRPV1 marks synaptic segregation of multiple convergent afferents at the rat medial solitary tract nucleus. PLoS One 2011;6. https://doi.org/10.1371/journal.pone.0025015.
[99] Shoudai K, Peters JH, McDougall SJ, Fawley JA, Andresen MC. Thermally active TRPV1 tonically drives central spontaneous glutamate release. J Neurosci 2010; 30:14470–5. https://doi.org/10.1523/JNEUROSCI.2557-10.2010.
[100] Doyle MW, Bailey TW, Jin YH, Andresen MC. Vanilloid receptors presynaptically modulate cranial visceral afferent synaptic transmission in nucleus tractus solitarius. J Neurosci 2002;22:8222–9. https://doi.org/10.1523/jneurosci.22-18-08222.2002.
[101] Dantas RO, Kern MK, Massey BT, Dodds WJ, Kahrilas PJ, Brasseur JG, et al. Effect of swallowed bolus variables on oral and pharyngeal phases of swallowing. Am J Physiol - Gastrointest Liver Physiol 1990;258:G675–81. https://doi.org/10.1152/ajpgi.1990.258.5.g675.
[102] Rofes L, Arreola V, Mukherjee R, Swanson J, Clavé P. The effects of a xanthan gum-based thickener on the swallowing function of patients with dysphagia. Aliment Pharm Ther 2014;39:1169–79. https://doi.org/10.1111/apt.12696.
[103] Tomsen N, Ortega O, Alvarez-Berdugo D, Rofes L, Clavé P. A comparative study on the effect of acute pharyngeal stimulation with TRP agonists on the biomechanics and neurophysiology of swallow response in patients with oropharyngeal dysphagia. Int J Mol Sci 2022;23:10773. https://doi.org/10.3390/ijms231810773.
[104] Shim JS, Oh BM, Han TR. Factors associated with compliance with viscosity-modified diet among dysphagic patients. Ann Rehabil Med 2013;37:628–32. https://doi.org/10.5535/arm.2013.37.5.628.
[105] Rosenvinge SK, Starke ID. Improving care for patients with dysphagia. Age Ageing 2005;34:587–93. https://doi.org/10.1093/ageing/afi187.
[106] Fiszman S, Laguna L. Food design for safer swallowing: focusing on texture-modified diets and sensory stimulation of swallowing via transient receptor potential activation. Curr Opin Food Sci 2023;50:101000. https://doi.org/10.1016/j.cofs.2023.101000.