Targeting Chemosensitive Channels for Dysphagia

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Swallowing is a physiological process that transports ingested foods, liquids, and saliva from the oral cavity into the stomach. Difficulty in the oropharyngeal swallowing process or oropharyngeal dysphagia is a major health problem. There is no established pharmacological therapy for the management of oropharyngeal dysphagia. Studies have suggested that the current clinical management of oropharyngeal dysphagia has limited effectiveness for recovering swallowing physiology and for promoting neuroplasticity in swallowing-related neuronal networks. The peripheral chemical neurostimulation strategy is one of the innovative strategies, and targets chemosensory ion channels expressed in peripheral swallowing-related regions. A considerable number of animal and human studies, including randomized clinical trials in patients with oropharyngeal dysphagia, have reported improvements in the efficacy, safety, and physiology of swallowing using this strategy. There is also evidence that neuroplasticity is promoted in swallowing-related neuronal networks with this strategy. The targeting of chemosensory ion channels in peripheral swallowing-related regions may therefore be a promising pharmacological treatment strategy for the management of oropharyngeal dysphagia.

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1. Introduction

Difficulties in the process of swallowing are termed dysphagia. Swallowing difficulties often lead to severe complications, such as pulmonary aspiration, malnutrition, dehydration, and pneumonia, which have high mortality rates [1][2][3][4][5][6][7]. Generally, dysphagia is divided into oropharyngeal and esophageal subtypes based on the location of the swallowing difficulty [8][9][10]. In oropharyngeal dysphagia, difficulty arises when transporting the food bolus or liquid from the oral cavity to the esophagus, while in esophageal dysphagia, the impedance occurs in the esophagus itself [8][9][10]. Oropharyngeal dysphagia is more prevalent and more severe than esophageal dysphagia [11]. In oropharyngeal dysphagia, patients have difficulties with evoking swallowing. Triggering of the swallow is often delayed, leading to impaired safety of swallowing. If the swallow response is not evoked at the correct time, the airways may remain open during swallowing. This can allow the entry of food particles or liquids into the laryngeal vestibule above the vocal folds (termed penetration,) or even deep into the airway below the vocal folds (termed aspiration), and may lead to aspiration pneumonia[12][13]. Airway penetration and aspiration are caused by a delayed laryngeal vestibule closure time and slow hyoid motion [1][14]. Impaired safety of swallowing with bolus penetration occurs in more than half of all patients with oropharyngeal dysphagia, and approximately 20–25% of

these patients present aspiration into the airway [1][15][16]. The inability to swallow efficiently can also lead to the presence of bolus residues in the oropharyngeal region (termed oropharyngeal residues), which causes the sensation of having food stuck in the oral cavity or throat regions [17][18]. Oropharyngeal residues occur because of weak bolus propulsion forces and impaired pharyngeal clearance [1][14].

There are many causes of oropharyngeal dysphagia, including neurovascular accidents (e.g., stroke or head injury), neurodegenerative diseases (e.g., Parkinson's disease, dementia, amyotrophic lateral sclerosis, multiple sclerosis, or Alzheimer's disease), neuromuscular problems (e.g., polymyositis/dermatomyositis or myasthenia gravis), and local lesions (e.g., head and neck tumors, surgical resection of the oropharynx/larynx, or radiation injury) [17][18][19]. More than half of all stroke patients and around 30% of traumatic brain injury patients develop some kind of swallowing dysfunction. In addition, approximately 50–80% of patients with Parkinson's disease, Alzheimer's disease, and dementia have oropharyngeal dysphagia [7][13][20][21][22]. Many older people also develop oropharyngeal dysphagia [17][18][23][24][25][26]. The prevalence of oropharyngeal dysphagia among institutionalized aged patients is more than 50%, while it is approximately 30% among the general older population [3][4][5][6][7][27][28][29][30].

2. Management of Oropharyngeal Dysphagia

2.1 Compensatory Strategies and Swallowing Exercises/Maneuvers

There is no established pharmacological therapy for the management of oropharyngeal dysphagia [31][32]. Currently, its clinical management is mainly focused on compensatory strategies and swallowing exercises/maneuvers [23][33][34][35]. Common compensatory strategies include modification of the properties of the bolus to be swallowed (e.g., changing the volume, viscosity, or texture of the bolus), and the adoption of different postures before swallowing (e.g., chin tuck or head tilt) [23][33][34][35][36][37][38]. Such compensatory strategies are short-term adjustments that aim to compensate for the swallowing difficulty, but they do not usually change the impaired swallowing physiology or promote the recovery of swallowing function in patients with oropharyngeal dysphagia [33][34][38][39]. Thickeners are often used to increase the viscosity of the bolus, to reduce penetration or aspiration [14][16][40]. Although, increasing the viscosity of the bolus using thickeners can improve swallowing safety, studies have reported that it also increases the amount of oropharyngeal residue [14][16][41][42][43]. Thickeners also have poor palatability, leading to poor compliance by patients [16][41]. Increasing the bolus volume has been reported to increase penetration and aspiration, along with increased amounts of oral [44] and pharyngeal residues, during swallowing in neurogenic oropharyngeal dysphagia patients [14][44]. Some common swallowing exercises/maneuvers include tongue exercises, jaw exercises, effortful swallow exercises, and Mendelsohn maneuvers (voluntarily holding the larynx in an elevated position). The aims of these exercises/maneuvers are to improve the efficacy of swallowing-related muscles, improve the motion of the bolus, and promote modest neuroplastic changes (i.e., the reorganization of neural connections) [34][36][37][38]. Although both compensatory strategies and swallowing exercises/maneuvers are widely used in clinical practice, the evidence to support their effectiveness is often limited [14][16][34][36][37][38][40][45][46][47][48].

2.2 Neurostimulation or Sensory Stimulation Strategies

In addition to compensatory strategies and swallowing exercises/maneuvers, neurostimulation or sensory stimulation strategies have also been investigated for the management of oropharyngeal dysphagia, although they have not yet become part of mainstream clinical practice [34][36][45][46][47][48][49]. In these strategies, stimuli are applied to central (cortical) or peripheral swallowing-related regions. In central neurostimulation strategies, transcranial magnetic stimulation, or transcranial direct current stimulation is applied to the brain to activate the swallowing-related motor cortex and corticobulbar pathways [34][50][51][52][53][54]. These strategies have shown promising results in stroke patients with oropharyngeal dysphagia [50][51][52][53][55][56]; however, to conduct these therapies (especially transcranial magnetic stimulation), specific and expensive equipment and well-trained professionals are required [57][58]. In peripheral neurostimulation/sensory stimulation strategies, various types of sensory stimuli (e.g., mechanical, thermal, electrical, or chemical) are applied to the oropharyngeal regions. These stimuli increase the sensory inputs to the swallowing center of the brainstem, as well as to the swallowing-related sensory cortex via the sensory nerves that innervate these regions, and thus improve swallowing function [34][49][59][60][61].

3.Targeting Chemosensory Ion Channels to Improve Swallowing Function

Table 1. Animal studies investigating the effects of targeting chemosensory ion channels on swallowing.

Targeting Channels	Agonists and Its Application	Animals	Mode of Application	Effects on Swallowing	Ref.
TRPV1	Capsaicin solution (25 μM) into the laryngopharynx and associated laryngeal regions	Rats	Acute	1. Capsaicin triggered a greater number of swallowing reflexes compared to distilled water/saline/vehicle; 2. Capsaicin shortened the intervals between the evoked swallowing reflexes compared to distilled water/saline/vehicle; 3. Prior topical application of a TRPV1 antagonist significantly reduced the number of capsaicin-induced	[62]

				swallowing reflexes and lengthened the intervals between the evoked reflexes.	
	Capsaicin solution (10 μM) into the larynx	Guinea pigs	Acute	Capsaicin triggered a greater number of swallowing reflexes compared to saline.	[63]
	Capsaicin solution (10 μM) on the vocal folds	Rats	Acute	Capsaicin triggered a considerable number of swallowing reflexes.	[64] [65]
	Capsaicin solution (600 nM) into the pharyngolaryngeal region	Rats (a dysphagia model)	Acute	Capsaicin improved the triggering of swallowing reflexes compared to that of distilled water.	[66]
TRPM8	Menthol solution (50 mM) into the laryngopharynx and associated laryngeal regions	Rats	Acute	1. Menthol triggered a greater number of swallowing reflexes compared to distilled water/saline/vehicle; 2. Menthol shortened the intervals between the evoked reflexes compared to distilled water/saline/vehicle; 3. Prior topical application of a TRPM8 antagonist significantly reduced the	[62]

				number of menthol-induced swallowing reflexes and lengthened the intervals between the evoked reflexes.	
ASIC3	Guanidine-4-methylquinazoline (GMQ) solution (0.5 to 10 mM) into the laryngopharynx and associated laryngeal regions	Rats	Acute	1. GMQ dose-dependently facilitated the triggering of swallowing reflex; 2. Prior topical application of an ASIC3 antagonist significantly reduced the number of GMQ-induced swallowing reflexes and lengthened the intervals between the evoked reflexes.	[67]
	Agmatine (50 mM to 2 M) solutions into the laryngopharynx and associated laryngeal regions	Rats	Acute	1. Agmatine dose-dependently facilitated the triggering of swallowing reflex; 2. Prior topical application of an ASIC3 antagonist significantly reduced the number of agmatine-induced swallowing reflexes and lengthened the intervals between the evoked reflexes.	[67]

ASICs and TRPV1	Acetic acid (5 to 30 mM), citric acid (5 to 30 mM) solutions into the pharyngolaryngeal region	Rats	Acute	Acetic acid and citric acid evoked a greater number of swallowing reflexes compared to distilled water.	[68]
	Citric acid solution (10 mM) into the pharyngolaryngeal region	Rats (a dysphagia model)	Acute	Citric acid solution improved the triggering swallowing reflexes compared to that of distilled water.	[66]

4. Conclusions

The advantages of the peripheral chemical neurostimulation strategy are that it does not require specific costly equipment and is relatively cheap and easy to conduct, and patient compliance may also be good. Patients are not required to swallow tablets or capsules; rather, the channel agonists can be mixed with ingestible boluses. Because patients with oropharyngeal dysphagia often face difficulties in swallowing tablets or capsules [69][70], this advantage may provide added benefits in terms of patient compliance. In a considerable number of human studies, low concentrations of natural agonists of some TRPs (e.g., capsaicin and piperine) have been mixed with ingestible boluses to improve swallowing functions (Table 2). These natural agonists are phytochemicals found in culinary herbs and spices, and are advantageous because they may not have serious side effects at low concentrations. Many phytochemicals and active compounds of various botanicals can activate TRPs [71], and therefore have the potential to facilitate swallowing. In future studies, phytochemicals of various botanicals should be investigated in animal and human trials to investigate their potency, specificity, and dose of action to improve swallowing functions. The TRP family has many members, but only TRPV1, TRPA1, and TRPM8 channels have so far been targeted in studies of dysphagia management. The expression of other TRPs (e.g., TRPV2, TRPV4, and TRPM3) has been reported in swallowing-related regions and ganglia [72][73][74][75]. Thus, the functional roles of these TRPs in swallowing processes need to be investigated in future research, as well as whether they can be targeted for dysphagia management. Along with TRPs, other chemosensory ion channels (e.g., ASICs and purinergic channels) can also be targeted. Highly potent synthetic agonists of these channels can be considered in basic research; however, their safety needs to be assured before they can be used in clinical trials.

Currently, the effect of long-term use of peripheral chemical neurostimulation strategy is unknown. Therefore, whether efficacy is retained in long-term agonist supplementation, and the possible development of adaptation or desensitization, needs to be studied in long-term randomized, controlled, multi-center trials of large numbers of patients with oropharyngeal dysphagia. Understanding the maintenance capability of neuroplasticity over time with

short- or mid-term supplementation is also important. Furthermore, patient phenotype is another important issue to be considered. The etiology of oropharyngeal dysphagia and its accompanying health conditions can vary among patients; therefore, same treatment strategy may not be effective for every patient phenotype [36][76][77]. Although patient recruitment may be challenging, clinical trials with large numbers of patients with the same phenotypes need to be conducted, to understand the effectiveness of different treatment strategies within the same patient phenotype. Studies combining the peripheral chemosensory ion channel activation strategy with other promising treatment strategies (e.g., cortical neurostimulation or pharyngeal electrical stimulation) may also need to be conducted.

Table 2. Human studies investigating the effects of targeting chemosensory ion channels on swallowing.

Targeting Channels	Agonists and Its Application	Patients/Participants	Mode of Application	Effects on Swallowing	Ref.
TRPV1	Capsaicin (1 nM to 1 μM) solution into the pharyngeal region	Aged patients with cerebrovascular diseases or dementia presenting oropharyngeal dysphagia	Acute	Capsaicin solution dose-dependently reduced the latency to trigger a swallow response.	[78]
	Capsaicinoid (150 μM) containing nectar bolus ingestion	Aged patients presenting oropharyngeal dysphagia	Acute	1. Laryngeal vestibule closure time during swallowing reduced; 2. Upper esophageal sphincter opening time during swallowing reduced; 3. Time for maximal vertical movement	[79]

			of the hyoid bone and larynx during swallowing reduced; 4. Prevalence of laryngeal penetration during swallowing reduced; 5. Prevalence of pharyngeal residue of bolus during swallowing reduced.	
Capsaicinoid (150 μM) containing nectar bolus ingestion	Aged/stroke/neurodegenerative disease patients presenting oropharyngeal dysphagia	Acute	1. Laryngeal vestibule closure time during swallowing reduced; 2. Prevalence of laryngeal penetration during swallowing reduced; 3. Prevalence of pharyngeal residue of bolus during swallowing reduced; 4. Bolus propulsion velocity during	[80]

			swallowing increased.	
Capsiate (1–100 nM) into the pharyngeal region	Patients with history of aspiration pneumonia presenting oropharyngeal dysphagia	Acute	Capsiate dose-dependently reduced the latency to trigger a swallow response.	[81]
Capsaicinoid (10 μM) containing nectar bolus ingestion	Aged patients presenting oropharyngeal dysphagia	Chronic (three times/day, before meals for 10 days)	1. Laryngeal vestibule closure time during swallowing reduced; 2. Score of the penetration-aspiration scale lowered; 3. Amplitude of cortical sensorial response to pharyngeal electrical stimulation increased; 4. Latency to evoke cortical sensorial response to pharyngeal electrical stimulation decreased.	[82]
Capsaicin containing	Healthy participants	Chronic	Latency to trigger a swallow response	[83]

	pickled cabbage (1.5 μg/10 g) ingestion		(before every major meal/day for 20 days)	reduced	
	Capsaicin containing lozenges (1.5 μg/lozenge)	Aged patients with cerebrovascular diseases presenting oropharyngeal dysphagia	Chronic (before every major meal/day for 4 weeks)	Latency to trigger a swallow response reduced.	[84]
	Capsaicin containing thin film food (0.75 μg/film) ingestion	Aged patients presenting oropharyngeal dysphagia	Chronic (before every major meal/day for 1 week)	1. Duration of cervical esophageal opening during swallowing shortened; 2. Symptoms of oropharyngeal dysphagia reduced; 3. Substance P concentration in saliva increased in patients who showed improvement of swallowing.	[85]
	Capsaicin (150 μM) containing nectar bolus ingestion along with cold thermal tactile stimulation	Aged patients with history of stroke presenting oropharyngeal dysphagia	Chronic (three times/day, before meals for 3 weeks)	Swallowing function improved assessed by swallowing assessment tools.	[86]

	Capsaicinoid (10 μM) containing nectar bolus ingestion	Aged patients presenting oropharyngeal dysphagia	Chronic (three times/day, before meals for 10 days)	The swallowing safety improved evidenced by reduction of the prevalence of aspiration and lowering the score in penetration-aspiration scale.	[87]
	Capsaicin (0.5 g of 0.025%) containing ointment into the ear canal	Aged patients presenting oropharyngeal dysphagia	Acute and chronic (once daily for 7 days)	Swallowing function improved.	[88]
	Menthol solution (100 μm to 10 mM) into the pharyngeal region	Aged patients presenting oropharyngeal dysphagia	Acute	Menthol dose-dependently reduced the latency to trigger a swallow response.	[89]
TRPM8	Menthol (1 and 10 mM) containing nectar bolus ingestion	Aged/stroke/neurodegenerative diseases patients presenting oropharyngeal dysphagia	Acute	1. Laryngeal vestibule closure time during swallowing reduced; 2. Prevalence of laryngeal penetration during swallowing reduced.	[43]

TRPA1					
	Cinnamaldehyde (756.6 μM) and zinc (70 μM) containing nectar bolus ingestion	Aged/stroke/neurodegenerative diseases patients presenting oropharyngeal dysphagia	Acute	1. Laryngeal vestibule closure time during swallowing reduced; 2. Upper esophageal opening time during swallowing reduced; 3. Score in penetration-aspiration scale lowered; 4. Frequency of safe swallows increased; 5. Latency of evoking cortical response to pharyngeal electrical stimulation shortened.	[90]
	Citral (1.6 mM) containing nectar bolus ingestion	Aged/stroke/neurodegenerative diseases patients presenting oropharyngeal dysphagia	Acute	1. Laryngeal vestibule closure time during swallowing reduced; 2. Upper esophageal opening time during	[90]

				swallowing reduced.	
TRPV1 and TRPA1	Piperine (150 μM and 1 mM) containing nectar bolus ingestion	Aged/stroke/neurodegenerative diseases patients presenting oropharyngeal dysphagia	Acute	1. Laryngeal vestibule closure time during swallowing reduced; 2. Time required for maximum anterior extension of hyoid bone during swallowing reduced; 3. Score in penetration aspiration scale lowered; 4. Prevalence of laryngeal penetration during swallowing reduced.	[91]
	Black pepper oil (a volatile compound) (100 μL for 1 min) to the nostrils with a paper stick for inhalation.	Aged patients with cerebrovascular diseases presenting oropharyngeal dysphagia	Acute	Latency to trigger a swallow response for distilled water reduced.	[92]
	Piperine (150 μM and 1 mM) containing	Aged/stroke/neurodegenerative diseases patients presenting oropharyngeal dysphagia	Acute	1. Laryngeal vestibule closure time during	[43]

nectar bolus ingestion			swallowing reduced; 2. Prevalence of penetration during swallowing reduced; 3. Bolus propulsion velocity during swallowing increased.	
Black pepper oil (a volatile compound) (100 μL for 1 min) to the nostrils with a paper stick for inhalation.	Aged patients with cerebrovascular diseases presenting oropharyngeal dysphagia	Chronic (three times/day, before meals for 30 days)	1. Latency to trigger a swallow response for distilled water reduced; 2. Serum substance P level increased; 3. Regional cerebral blood flow in right orbitofrontal and left insular cortex increased.	[92]
Black pepper oil (a volatile compound) (100 μL for 1 min) to the nostrils with a paper stick for inhalation.	Pediatric patients with severe neurological disorders often receiving tube feeding	Chronic (three times/day, before meals for 3 months)	1. The amount of oral intake of foods by the patients increased; 2. Swallowing-related movements increased.	[93]

TRPV1, TRPA1 and TRPV3	Vanillin (a volatile compound), (flow rate 7 L/min for 200 ms) delivered ortho-and retro-nasally	Healthy participants	Acute	The frequency of swallowing for continuous intraoral sweet stimuli (glucose) increased in case of retro-nasal delivery.	[94]
TRPA1 and TRPM8	Citral (1.6 mM) and isopulegol (1.3 mM) containing nectar bolus ingestion	Aged/stroke/neurodegenerative diseases patients presenting oropharyngeal dysphagia	Acute	Upper esophageal opening time during swallowing reduced.	[90]
ASICs and TRPV1	Citric acid (2.7% or 128 mM) containing liquid bolus ingestion	Aged patients with neurological diseases presenting oropharyngeal dysphagia	Acute	Prevalence of aspiration and penetration during swallowing reduced.	[95]
	Lemon juice containing barium liquid bolus (1:1) ingestion	Patients with strokes and neurological diseases presenting oropharyngeal dysphagia	Acute	1. Swallow onset time reduced; 2. Time required to trigger the pharyngeal swallow (pharyngeal delay time) reduced; 3. Frequency of aspiration reduced; 4. Oropharyngeal swallow efficiency increased.	[44]

Lemon juice containing barium liquid bolus (1:1) ingestion	Healthy participants and head and neck cancer patients	Acute	Pharyngeal transit time reduced.	[96]
Citric acid (80 mM) delivered on the tongue	Healthy participants	Acute	1. Frequency of swallowing increased; 2. Hemodynamic responses in the cortical swallowing-related areas prolonged.	[97]
Lemon juice application on the tongue along with nasal inhalation of lemon juice odor	Healthy participants	Acute	Motor evoked potential from the submental muscles increased during volitional swallowing induced by transcranial magnetic stimulation.	[98]
Citric acid solution (20 mM) ingestion	Healthy participants	Acute	Activity of submental muscle during swallowing increased.	[99]
Citric acid solution (2.7% or 128 mM) ingestion	Healthy participants	Acute	1. Amplitude of anterior tongue-palate pressure	[100]

				during swallowing increased; 2. Activity of submental muscles during swallowing increased.	
	Lemon juice (10%) solution ingestion (4°C before delivery)	Healthy participants and stroke patients with and without oropharyngeal dysphagia	Acute	1. Inter-swallow interval shortened in healthy participants of <60 years of age; 2. Inter-swallow interval unaffected in stroke patients; 3. Velocity and capacity of swallowing reduced both in healthy individuals and stroke patients.	[101]
	Lemon juice delivered on tongue	Healthy participants	Acute	1. Number of swallowing increased; 2. Salivation increased; 3. Amount of salivation correlated with the number of swallowing.	[102]

	Acetic acid (10 and 100 mM) applied on the posterior part of the tongue	Healthy participants	Acute	Latency to trigger swallowing prolonged compared to that of water.	[103]
	Citric acid (2.7%) solution ingestion	Healthy participants	Acute	Lingual pressure during swallowing increased.	[104]
	Citric acid (10%) solution ingestion	Healthy participants	Acute	Speed of swallowing reduced compared to that of water.	[105]
	Citric acid containing gelatin cubes (4.4 g of citric acid in 200 ml of gelatin) chewing and ingestion	Healthy participants	Acute	1. Oral preparation time during swallowing accelerated; 2. Amplitude of submental muscle activity during swallowing increased; 3. Duration of submental muscle activity during swallowing reduced.	[106]
	Lemon water (50%) solution ingestion	Healthy participants	Acute	1. Activity of submental muscles during swallowing increased;	[107]

				2. Onset time of activation of the submental muscles closely approximated.	
	Lemon juice (a drop of 100% lemon juice in the anterior faucial pillar) + cold mechanical stimuli using a probe (around 8–9 °C) before swallowing of water	Healthy participants	Acute	Latency to trigger swallowing reduced.	[108]
	Lemon juice (1:16, mixed with water) ingestion	Healthy participants	Acute	Onset time of activation of the submental and infrahyoid muscles shortened.	[109]

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