Published in final edited form as:

Curr Phys Med Rehabil Rep. 2023 June ; 11(2): 188–198. doi:10.1007/s40141-023-00393-8.

Dysphagia in Parkinson Disease: Part II—Current Treatment Options and Insights from Animal Research

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Abstract

Purpose of Review—Dysphagia is highly prevalent in Parkinson disease (PD) but is not typically identified nor treated until later in the disease process. This review summarizes current pharmacological, surgical, and behavioral treatments for PD-associated dysphagia and contributions from translational animal research.

Recent Findings—Swallowing is a complex physiologic process controlled by multiple brain regions and neurotransmitter systems. As such, interventions that target nigrostriatal dopamine dysfunction have limited or detrimental effects on swallowing outcomes. Behavioral interventions can help target PD-associated dysphagia in *mid-to-late* stages. Animal research is necessary to refine treatments and useful in studying *prodromal* dysphagia.

Summary—Dysphagia is an early, common, and debilitating sign of PD. Current pharmacological and surgical interventions are not effective in ameliorating swallowing

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Conflict of Interest Dr. Michelle R. Ciucci is on the board of directors of the National Foundation of Swallowing Disorders (NFOSD) and receives no compensation as member of the board of directors.

Human and Animal Rights and Informed Consent This article does not contain any studies with human participants or animals performed by any of the authors.

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dysfunction; behavioral intervention remains the most effective approach for dysphagia treatment. Animal research has advanced our understanding of mechanisms underlying PD and PD-associated dysphagia, and continues to show translational promise for the study of dysphagia treatment options.

Keywords

Parkinson disease; Swallowing; Dysphagia; Pathophysiology; Treatment; Animal models

Introduction

Since its discovery, Parkinson disease (PD) has been known as a disease of the central nervous system, one that results in nigrostriatal dopamine depletion and hallmark motor disturbances (i.e., bradykinesia, resting tremor, rigidity, postural instability). As such, most treatment efforts have been dopamine-centric, aimed at ameliorating these debilitating hallmark motor signs of disease by targeting dopamine depletion in the brain. The disease, however, is now known to be a whole-body disease that begins prior to nigrostriatal involvement and motor sign development. In fact, hallmark motor signs of disease likely represent the mid-to-late stages of disease. Although the etiology is not yet fully understood, it is now accepted that PD onset may occur decades prior to diagnosis.

Some of the earliest noted signs of PD are autonomic, non-motor, and “other” motor features. These include gastrointestinal dysfunction, hyposmia, sleep disturbances, depression, diplopia, anxiety, cardiac dysautonomia, hypophonia, and, the focus of this review, dysphagia [1]. Dysphagia contributes to malnutrition, dehydration, economic burden, decreased quality of life, and mortality [2, 3, 4] in this population. The oral, pharyngeal, and esophageal stages of swallowing may be impaired and ultimately affect the efficient and safe transport of food, liquid, and/or saliva (bolus) from mouth to stomach, which can lead to inefficient oral intake and airway compromise (e.g., aspiration). In fact, aspiration pneumonia is the leading cause of death in PD [3, 4].

Despite the prevalence and impact on patient quality of life, there is limited research on how best to treat dysphagia, as well as other non-motor PD-associated signs. In fact, most of these features do not respond to dopamine replacement and are likely affected by other neurotransmitter systems [5, 6], rendering current pharmacologic and surgical interventions ineffective for the early and holistic treatment of PD. Studies examining mechanisms underlying non-motor signs of PD have unveiled the complexity of PD in terms of catecholaminergic involvement. Different neurotransmitter systems beyond dopamine—including cholinergic, noradrenergic, and serotonergic—are compromised, implicated early, and contribute to dysfunction [1, 7].

It is also important to note that PD is heterogeneous in its presentation, further complicating our understanding of PD in the early stages and how to approach treatment, especially from a preventative standpoint. Leading hypotheses point to several subtypes of PD based on clinical presentation (including motor and non-motor presentation), as well as age of onset, sex, genetics, and major pathologic hallmarks [7]. Improved understanding of the mechanisms underlying differences among patients will aid in the development of

individualized therapies. For a detailed review of PD pathophysiology, the heterogeneity of presentation, and current diagnostic approaches, please refer to the complementary article in this issue “Dysphagia in Parkinson disease: Part I—Pathophysiology and Treatment Practices.”

As with other non-classical signs and symptoms, the pathophysiology underlying swallowing dysfunction in PD is poorly understood. Current understanding points to both dopaminergic and non-dopaminergic mechanisms being involved in PD-related swallow dysfunction, with the latter likely being implicated sooner [1]. Moreover, alpha-synuclein (α-syn) aggregates (a hallmark protein pathology in PD) have been found throughout the body, including in regions associated with swallowing (e.g., in salivary glands [8]); however, their direct impact on swallow function is not yet fully understood. Despite many differences in the onset, progression, and clinical manifestation of PD, dysphagia frequently occurs at some point in the disease process, with over 90% of people with PD being affected, and often leads to aspiration pneumonia, the leading cause of death in this population [2–4]. Moreover, changes in swallowing occur early in the disease process, often in the prodromal stage prior to diagnosis; however, given co-occurring sensory deficits in PD, individuals are often unaware of their swallowing changes until the disease progresses and severity of the dysfunction worsens.

Behavioral interventions remain the gold standard for dysphagia treatment, as current pharmacological and surgical interventions are not effective in ameliorating swallowing dysfunction [9, 10]. Despite research advancements, our understanding of mechanisms underlying dysphagia in PD, especially in the prodromal stage, is incomplete. This further complicates our ability to diagnose, treat, and study PD-associated dysphagia at its onset. There is a significant role for translational research, including animal models, for studying these underlying mechanisms as well as the efficacy of interventions that are otherwise impossible to conduct in humans. Moreover, research in human participants is limited by the inability to assess central and peripheral tissue changes during disease or after intervention, which is feasible with use of animal models. The contributions of animal models to the PD literature will be discussed in this review, as well as current treatment practices, existing gaps in knowledge, and future directions for PD-associated dysphagia research and clinical practice.

Treatment

Management of PD is categorized into three main intervention approaches: pharmacological, surgical, and behavioral. These interventions can be prescribed concurrently and are based on patient need, which changes over time. Most medical interventions are not directly prescribed for dysphagia management and their primary and secondary effects may have positive, negative, or no effect on swallowing function. Here, we will focus on commonly prescribed medication and neurosurgery for PD in general and how these affect swallow function, and then specifically address treatments for dysphagia and saliva management.

Pharmacological

The current standard of care for pharmacological treatment of PD predominantly targets the nigrostriatal dopamine system through dopamine precursors (e.g., levodopa) [11], clearance enzyme inhibitors (e.g., carbidopa) [11], and dopamine receptor agonists (e.g., pramipexole) [12]. Because dopamine does not cross the blood–brain barrier, dopamine precursors such as levodopa are administered. To prevent levodopa from synthesizing into dopamine in the periphery prior to crossing the blood–brain barrier, carbidopa is often prescribed with levodopa. Combining levodopa with a monoamine oxidase inhibitor (carbidopa) also prevents premature levodopa break-down and clearance, and diminishes side effects associated with increased dopamine in the peripheral tissues [13]. In some cases, dopamine agonists may be clinically indicated as first-line treatment [13]. Pramipexole is clinically efficacious both alone and with levodopa for treating PD motor dysfunction [13]. However, treatments aimed at increasing dopamine signaling are not beneficial for PD-associated dysphagia [14, 15] and levodopa specifically shows limited benefit or adverse effects on swallowing function [16]. As such, it is recommended to assess swallowing function while controlling for drug effects (e.g., FEES-Levodopa-Test) [17].

Surgical

Deep brain stimulation (DBS) is a surgical treatment option for PD [18]. The procedure involves unilateral or bilateral surgical implantation of electrodes that generate electrical impulses in brain regions, most commonly the subthalamic nucleus (STN) or globus pallidus internus (GBi) [19]. Neither STN or GBi DBS demonstrates improved swallow safety, with some patients even worsening after treatment [20, 21]. Evidence shows a DBS benefit bias towards swallow efficiency, but not safety [22]. Novel stimulation-based treatments for PD-associated dysphagia include DBS for non-STN regions [23], high frequency STN-DBS, and transcranial magnetic stimulation [24]. Work is still ongoing and additional brain regions and stimulation parameters should be considered for optimizing dysphagia treatment.

Behavioral

Behavioral approaches remain the gold standard treatment for PD-associated dysphagia. Interventions are characterized as restorative, compensatory, and adaptive. This review will focus primarily on restorative interventions, as the most recent PD-specific research on the other intervention types is currently sparse or studies were performed on populations beyond PD [25].

Rehabilitative interventions are exercises intended to improve swallow physiology without conscious manipulation of bolus flow or modification. These can be strength-based or skill-based, depending on the physiological goal. Respiratory muscle strength training (RMST) is a strength-based exercise approach which is among the most widely researched treatments for PD-associated dysphagia. Expiratory muscle strength training (EMST) is currently the most researched approach and was originally developed to address reduced expiratory airflow commonly seen in PD [26]. The EMST device is a small tube with manually adjustable valving that allows air to pass through with progressively increased pressure thresholds. The physiological rationale for this exercise program is to provide resistance to the muscles of expiration to facilitate successful airway clearance [27]. EMST elicits

improvements in respiratory volumes [28], expiratory pressures [29••, 30], cough physiology [31, 32], and penetration-aspiration outcomes [20, 28]. Inspiratory muscle strength training (IMST) focuses on the muscles of inspiration to facilitate a larger volume of inspired air for exhalation. Studies have demonstrated increased recruitment of swallowing-related musculature, including the submental muscles, soft palate, and pharynx [33, 34] through use of ultrasound [34], high-resolution manometry [33], and electromyography [33]. IMST reportedly improves inspiratory muscle endurance; moderately improves maximum inspiratory pressures, maximum phonation time, and peak subglottic pressure; and only trivially (standardized effect size of < 0.2) improves voluntary peak cough flow [30, 32, 35]. Despite promising findings from prior work, additional studies examining efficacy of RMST programs are needed to address heterogeneity of protocol, dosing, and outcome measure across disease stages [28].

Lee Silverman Voice Treatment (*LSVT-LOUD*®) is a well-established treatment program designed to maximize the perceptual characteristics of voice through hierarchical advancement of vocal load via high-effort phonatory tasks [36]. Given that voice and swallowing share many of the same central and peripheral structures, a few small studies have explored the effects of LSVT on swallowing function [37, 38]. El Sharkawi and colleagues found several improvements related to swallow function, including increased anterior-to-posterior lingual propulsion, increased tongue base retraction, decreased oral transit time, decreased oral residue percentage, reduced pharyngeal transit time, and increased oropharyngeal swallow efficiency [37]. Similarly, a study by Miles and colleagues revealed swallowing improvements to swallow function after LSVT including reduced pharyngeal residue, reduced pharyngeal area at rest, increased maximal opening of pharyngoesophageal segment (PES), and increased PES opening duration [38]. Further research is needed to corroborate these effects on a larger scale.

Other strength-based exercise programs have also been studied in PD. Neuromuscular electrical stimulation (NMES) applies surface electrodes to provide sub-cutaneous electrical stimulation to the muscles and is well-established as an intervention to promote muscle recovery from injury in the skeletal muscles [39]. NMES has emerged as a potential treatment modality for dysphagia. Two studies have assessed NMES in PD, with one demonstrating improvements in hyoid movement and penetration-aspiration scores compared to placebo [40] and the other concluding that NMES did not elicit any further benefits compared to traditional dysphagia therapy [41]. The efficacy of NMES for swallow function in PD remains unclear and further research is warranted to optimize stimulation parameters. Finally, lingual strengthening has been explored in combination with EMST in PD patients, revealing improvements in lingual strength and maintenance of function in regard to clinical swallowing measures [42].

Skill-based interventions are designed to train the patient to improve coordination necessary to complete a specific task, as opposed to increasing muscle strength. Promising effects of respiratory-swallow coordination training and voluntary cough skills are reported for respiratory-swallow coordination, penetration-aspiration, vallecular/pyriform residue, and overall dysphagia severity [43]. Another intervention—sensory-motor training for airway protection (smTAP)—improves measures of reflexive cough including flow rate, volume,

and urge-to-cough [29••]. Additionally, video-assisted swallow therapy (VAST), which uses endoscopy-facilitated biofeedback to encourage implicit modifications of swallowing physiology, has been assessed [44, 45]. VAST demonstrated improved pharyngeal clearance and SWAL-QOL scores [45]. Finally, the effects of air stacking have recently been applied to dysphagia therapy in PD [46]. Air stacking involves the manual over-insufflation of the lungs through use of an external insufflator, bypassing the restriction to inspiratory range of motion seen in PD, and capitalizing on the natural elasticity and recoil of the thoracic cavity [46]. Paired with EMST, air stacking elicits the most benefit to aspects of airway protection including reflexive and voluntary peak cough flow [32]. Despite PD affecting range of motion and coordination of swallowing/cough, behavioral interventions appear to be biased towards strength-based treatments [47]. More research is needed to determine the efficacy of skill-based interventions.

Surgical and pharmacological PD interventions are generally not designed to address other motor signs, such as dysphagia, and therefore are limited for or detrimental to swallowing outcomes. This may be, in part, due to the focus on basal ganglia-related dopamine systems and treatment of gross motor signs such as tremor. Because swallowing is a complex physiologic event that is controlled by multiple brain regions and neurotransmitter systems [14, 15, 48], identifying a treatment target (region of interest) is difficult. Although some behavioral interventions for dysphagia are promising, solid evidence remains limited by heterogeneity in patients, small sample sizes, and an overall lack of clinical trials. Most importantly, PD interventions are currently affected by limitations in timely diagnosis. There is a notable effort to shift toward a more proactive model of dysphagia rehabilitation in neurodegenerative populations [49]; however, proactive management of PD is not standard, as our understanding of prodromal PD is still developing.

Saliva

In addition to swallowing, changes to salivation are prevalent in PD across various stages of disease. Although distinct from dysphagia, salivary disturbances can greatly affect one’s swallow. About 50% of individuals with PD experience hyposalivation [50, 51] and xerostomia [50], and 50% experience sialorrhea [52]. Salivary flow in PD is complicated by commonly prescribed first-line medications. Clozapine [53] and levodopa [54] primarily increase salivary flow, while anticholinergic medications used to reduce tremor can result in xerostomia [55]. Sialorrhea is often managed with botulinum toxin injections to the parotid and submandibular glands to reduce salivary flow [56], whereas salivary replacements [57] and sialagogues [58] remain the most common treatments for xerostomia and hyposalivation. Although studies assessing non-pharmacological management of saliva-related deficits in PD are sparse [59], some evidence points to the short-term benefit of behavioral intervention [60] and the long-term benefit of radiotherapy for sialorrhea management [61]. Gum chewing has also been found to promote swallow frequency, which may be an effective strategy for secretion management in PD [62]. Additional research is needed to understand the methods to best manage these conditions considering the contradictory nature of treating xerostomia and sialorrhea.

Animal Research Related to PD-Associated Dysphagia

Human clinical research, especially with regard to dysphagia diagnosis and treatment, is limited by ethical constraint for rigorous placebo controls, inability to access tissues implicated in pathology, and heterogeneity inherent to PD (phenotype, onset, progression) and humans in general (age, diet, lifestyle, medical co-morbidities, medications, genetics, etc.). Furthermore, research typically begins after diagnosis and the ability to study prodromal- and early-stage PD is nearly impossible. Therefore, animal models offer better experimental control and the ability to study multiple aspects of disease pathology across disease progression. Selection of the model species is based on the relevant pathology and associated behavior. For swallowing specifically, rats, non-human primates, and pigs are commonly used, though the latter two have not been used for the study of PD-associated dysphagia treatment [63, 64]. Several approaches to modeling PD in animals include systemic and region-specific neurotoxin administration and genetic manipulation. Each model targets different mechanisms of PD, including, but not limited to, nigral dopaminergic cell death, mitochondrial dysfunction, oxidative stress, inflammation, and/or α-syn phosphorylation and aggregation, and should be carefully chosen based on the aspect of pathology that is relevant to the gap in knowledge/research question. Unfortunately, while some research has been conducted to understand the mechanisms underlying dysphagia in PD, there is little research assessing the efficacy of interventions in PD-specific animal models at this time. However, more comprehensive research has been published on the treatment of dysphagia in an aging rat model, discussed below. Because PD is a disease of aging and there is some overlap in swallowing dysfunction, aging models can inform PD models. Moreover, most research has been conducted in males (with a few exceptions) because of the confounds of estrogen, especially in rat models. For example, estrogen is neuroprotective against certain neurotoxins and the rapid (4 days) estrous cycle in rats and mice makes controlling for estrous cycle operations challenging. That being said, animal work is paramount for improving understanding of the mechanisms underlying dysphagia in PD and advancing diagnostic criteria and interventions for optimal dysphagia management.

Neurotoxin Models

Because swallowing deficits in PD are readily apparent in the mid-to-late stages, yet are generally unresponsive to dopamine replacement and DBS, the role of nigrostriatal dopamine depletion in dysphagia is unclear. As such, neurotoxin models can be used to study the effects of nigrostriatal dopamine depletion on oromotor and swallow function (tongue function, licking, chewing, oropharyngeal and esophageal swallowing). 6-Hydroxydopamine (OHDA), for example, is a catecholaminergic neurotoxin that induces neurodegeneration of the nigrostriatal dopamine system via intracerebral or systemic infusion [65–67]. After administration of 6-OHDA, rats demonstrate limb motor deficits, akin to the hallmark motor deficits seen in humans as a result of significant nigrostriatal dopamine depletion. Additionally, 6-OHDA administration in rats leads to swallow-specific changes, including altered tongue function (i.e., reduced tongue force [67], reduced lick force [65]), changes to chewing of uncooked pasta (i.e., reduced intensity, regularity, and rate of acoustic signal [68]), and impaired functional swallowing measured by videofluoroscopy (i.e., increased aberrant tongue movements, decreased bolus areas

[69]). These deficits affect swallowing safety and efficiency and translate to clinical findings of dysphagia in the mid-to-late stages of PD [3]. Other neurotoxins, including 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and the pesticide rotenone, also induce nigrostriatal dopamine depletion and have been used to assess mechanisms underlying swallowing dysfunction in PD. The neurotoxin MPTP, for example, induces nigral dopaminergic cell death via complex I inhibition and subsequent oxidative stress and apoptosis [63, 70]. MPTP-induced dopamine depletion in non-human primates causes a series of acute toxic effects with clinical implications including reduced ability to self-feed due to mobility impairments, reduced appetite, and dehydration [63, 71]; in minipigs, MPTP results in motor deficits (muscle rigidity, hypokinesia, abnormal coordination, and position of the limbs), as well as reduced food intake [72]. These models, however, have not been used as extensively as the 6-OHDA rodent in examining the efficacy of dysphagia treatments.

Tongue Exercise in the 6-OHDA Model

6-OHDA animal work reveals that targeted limb training can slow or prevent limb motor deficits and reduce vulnerability of dopaminergic neurons [73, 74, 75]. Based on these findings, the effects of targeted lingual training on tongue function were also assessed and revealed contrasting findings. Tongue training in rats' post-unilateral 6-OHDA administration resulted in improved tongue force and timing outcomes in a study conducted by Ciucci and colleagues [76]. These findings contrast with those of Plowman and colleagues; however, where progressive lingual resistance rehabilitation did not appear to improve cranial motor (lick) function, only limb motor rehabilitation improved limb motor functions [65]. It should be noted that methods differed slightly across these studies, including site of 6-OHDA infusion (medial forebrain bundle [76] vs. striatum [65]), schedule of water reward (variable ratio 5 schedule [76] vs. fixed-ratio 12 [65]), and the total number of weeks (4 weeks [76] vs. 6 weeks [65]) that rats underwent treatment for the rescue of tongue function. Both studies, however, revealed that tongue exercise was not associated with striatal dopamine content.

Taken together, findings reveal that nigrostriatal dopamine depletion *does* play a role in certain aspects of PD-associated dysphagia in the *mid-to-late stages* of disease when significant nigral dopamine is depleted, as evidenced by the development of oromotor deficits after neurotoxin administration. Additionally, targeted exercise may be useful in ameliorating swallowing deficits; however, the mechanisms underlying this rescue ought to be explored further. Moreover, given that swallowing is a complex sensorimotor process involving multiple systems, the use of neurotoxin models may not fully recapitulate swallow deficits as they appear in human PD. Neurotoxin models also exclude other prodromal, early, or later stage degeneration/pathology, which may be key to understanding *why* dopamine-based interventions are largely ineffective for the treatment of dysphagia in PD.

Genetic Models

Several genes have been linked to PD and have led to the development of genetic animal models. These genes include SNCA, GBA, LRRK2, PRKN, PINK1, and DJ-1, as reviewed elsewhere [77], which can be knocked out, knocked in, or overexpressed in animal models.

Genetic models have significantly improved our ability to study other mechanisms involved in the disease, especially in the prodromal stages of PD. Changes to sensorimotor function, including swallowing, occur up to 20 years prior to nigrostriatal dopamine depletion. Animal models that use genetic manipulations that are known to cause PD can model prodromal and early pathologic aspects of PD *prior* to nigrostriatal cell death. To date, most research related to swallowing has occurred in primarily two genetic models—DJ-1 and PINK1 knockout rats.

In humans, DJ-1 and PINK1 mutations are associated with autosomal recessive, early-onset PD. Both genes are implicated in protecting cells against oxidative stress and mitochondrial dysfunction. The deletion or mutation of DJ-1 leads to signs akin to the inherited early-onset form of PD which presents with rigidity, tremors, alterations to vocalizations, and cognitive decline [66]. The *DJ-1* knockout (−/−) genetic PD rat model has been used to study the prodromal and early-to-mid stages of disease (i.e., age 2–8 months) and shows oromotor and cranial sensorimotor deficits, including reduced tongue function regulation and impaired chewing [66, 78]. An important finding from this work is that there are significant correlations among limb motor and oromotor dysfunction and noradrenergic cell loss and tyrosine hydroxylase-immunoprotective (TH-ir) cell loss in the locus coeruleus [78]. The locus coeruleus is a brainstem nucleus that synthesizes noradrenaline and has projections to multiple brain regions, including those implicated in swallowing, mood, and cognitive function. In PD, the noradrenergic system is implicated early in the disease process [79•]. Loss of noradrenergic neurons exacerbates damage to dopaminergic neurons, while noradrenaline is anti-inflammatory and neuroprotective on dopaminergic degeneration [79•]. In PD, noradrenaline affects sensorimotor behaviors, including those of the upper airway (e.g., vocalization) [80]. As such, noradrenaline-based pharmacotherapies may be beneficial for PD, including for non-classical signs of disease, such as dysphagia.

Similarly, mutation of PINK1 (PTEN-induced putative kinase; *PARK6*) leads to mitochondrial dysfunction and progressive non-motor/other motor signs of disease, as well as α-syn aggregation and eventual nigrostriatal dopamine cell death, causing limb motor signs akin to sporadic PD [66, 81, 82, 83]. The *Pink1−/−* genetic rat model exhibits oromotor and early oral stage deficits that align with human clinical findings in PD [3, 84]. Deficits include decreased mastication rate [82, 84], as well as increased tongue press force, variability, and rate with increased amounts of α-syn in the genioglossus muscle and a change in muscle fiber composition in the styloglossus muscle [84, 85]. Additionally, *Pink1−/−* rats exhibit increased bolus area and bolus velocity [82], suggesting dyscoordination affecting swallow safety and efficiency [3, 82]. Like *DJ-1−/−* rats, *Pink1−/−* rats also show relationships between behavioral deficits and neuropathology. Correlations between decreased mastication rate and TH-ir counts in the locus coeruleus have been reported [82], as well as increased amounts of α-syn protein in the nucleus ambiguus [82] which is a key region in the swallow central pattern generator. Sex differences have also been found in the *Pink1−/−* genetic rat model, such as differences in limb motor deficits [83, 84] and cranial sensorimotor functions (e.g., vocalizations) [66, 83], but further research is needed to assess potential differences specific to swallowing function.

Overall, findings demonstrate that both central and peripheral pathologies in early stages of disease implicate critical mechanisms for functional oropharyngeal swallowing. These include neurotransmitter systems other than dopamine (e.g., norepinephrine), α-syn pathology, and mitochondrial dysfunction. Genetic models significantly contribute to our evolving understanding of PD pathology and swallowing dysfunction. Although the efficacy of behavioral dysphagia interventions has not yet been assessed in these genetic animal models, findings from this work may be foundational for refining treatment options to better treat swallow-specific deficits in PD.

Tongue Exercise in Aging Models

To date, studies assessing swallowing interventions in PD-specific animal models have been limited; however, aging models (especially rats) have been widely used to study the efficacy of dysphagia interventions and will be briefly described in this review, as well. It is known that with age, muscle composition and function changes, including swallow-related muscles such as the genioglossus (tongue) muscle. While tongue exercises are commonly prescribed to patients, the optimal dosing and exact effects on muscle properties are not fully understood. Tongue training and exercise methods have been used in rats as previously described [86, 87]. Studies reveal that, following progressive resistance tongue exercise, tongue forces increase [86, 88]. This positive change in tongue force generation post-exercise is seen across young, middle-aged, and old rat groups, as well [89]. In a study comparing different exercise doses (1, 3, or 5 day/week), 5 day/week intervention groups showed the greatest increase in tongue forces, and regardless of dose, tongue forces increased following exercise compared to sham groups [90]. Clinically, behavioral interventions may show promise in the short term, but lasting benefits of exercise are also poorly understood. As such, detraining protocols have also been implemented in rat studies and reveal that detraining does *not* eliminate improved tongue force following exercise, though decline in maintenance is seen in old (aged) groups compared to younger rats [88]. Whether these findings translate to a progressive degenerative model of PD, however, is not yet known. Since PD typically is a disease of aging and affects swallow function, this exercise approach is promising.

In terms of muscle biology, exercise appears to alter some properties, though changes are not as apparent to muscle biology as they are to function (e.g., force, as described above). Schaser and colleagues found brain-derived neurotrophic factor (BDNF) and receptor TrkB immunoreactivity levels in the rat hypoglossal nucleus to be positively cor-related with exercise in young and middle-aged rats. These associations, however, were weak in the older groups and in no-exercise controls, suggesting that other mechanisms may underlie the increased tongue forces seen post-exercise in older rats. In another study, 8 weeks of tongue exercise significantly increases tongue force as well as the variability of genioglossus (tongue) muscle fiber cross-sectional area [86]. This is in contrast to a more recent study, assessing the role of age and exercise on muscle fiber composition. While age was found to play a role in altering the proportion and size of type I (slow) and type II (fast) tongue muscle fibers, exercise did not alter tongue muscle fiber size or composition [90]. The tongue, however, includes many intrinsic and extrinsic muscles that serve different functions during swallowing [91], as well as speech [92] and airway patency [93]. As

such, consideration should be given to the intensity and duration of tongue training, as tongue muscles may naturally have increased endurance due to their multifunctional and frequent use. Tongue exercise was also shown to increase serotonin immunoreactivity in the hypoglossal nucleus, though this neurochemical change was only seen in young rats [94].

Existing Gaps in Knowledge and Future Directions

Despite dysphagia manifesting early in PD, treatment implementation typically occurs later in the disease process when features of dysphagia are more severe [95, 96, 97]. Additionally, our limited understanding of the underlying biologic mechanisms in the prodromal and early stage is a key hindrance to optimizing interventions, especially those that target prevention [98].

A major consideration in PD-associated dysphagia management is, in part, a consequence of the pharmacological and surgical treatments targeting the gross motor disturbances of the disease. These treatment options have been largely successful in managing limb motor and other gross motor functions [99]. Unfortunately, there are limited benefits to swallow function and, in some instances, worsen aspects of dysphagia [3, 17]. Advancements in surgical and pharmacological treatment options that can improve both gross motor and swallowing sensorimotor functions are necessary.

Different clinical presentations in terms of age of onset, phenotype, disease progression, and clinical management considering sex as an important biological variable have not yet been adequately addressed. Failure to substantially include females in previous research, including basic, translational, and clinical studies, has widened gaps in knowledge and minimizes the generalizability of current treatment approaches. The inclusion of females has been highly encouraged in recent years per NIH mandate [100]. This broader inclusion will aid in developing a more complete understanding of PD-associated dysphagia management, including responses to behavioral and pharmacological manipulations.

Conclusion

The pathophysiologic mechanisms that modulate swallow function, especially in the prodrome, are not well understood, and therefore diagnostic and treatment options remain suboptimal. Dopamine-based treatment paradigms aimed at improving gross motor function provide inconsistent benefits to the sensorimotor aspects of PD dysfunction. This encourages the idea that other neurotransmitter pathways in the CNS and PNS are likely involved and could be potential targets for future research to guide pharmacological, surgical, and behavioral treatment optimization. Behavioral treatments are currently the most effective treatment for dysphagia management in PD; however, benefits of these are still unclear and may be difficult to sustain as the disease progresses. Therefore, additional research that addresses these questions in current clinical approaches is necessary to develop and refine more targeted and sustained benefits in PD-related dysphagia. Animal research can contribute significantly to address these gaps in knowledge.

Funding

This work was supported by the National Institute on Deafness and Other Communication Disorders of the National Institutes of Health (T32DC009401, appointee: Krasko; R01 DC018584, Ciucci; R01 DC014358, Ciucci), the National Institute on Aging of the National Institutes of Health (1K76AG068590, Rogus-Pulia), the University of Wisconsin-Madison, and the William S. Middleton Veteran Affairs Hospital in Madison, WI; GRECC article no. 2023-XXX.

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