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Oro-Neuro collateral mutilation in Parkinson's disease

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Abstract
Parkinson's disease (PD) is a degenerative disorder of the central nervous system. Early in the disease, motor symptoms such as shaking, rigidity, slowness of movement, and difficulty with walking are noticed. These symptoms result from the death of cells in the *substantia nigra*. cell death is due to modification of some intracellular proteins into Lewy bodies; resulting in dopamine deficiency. Lewy bodies are abnormal aggregates of alpha-synuclein that develop inside nerve cells of the brain in PD. Lewy bodies could be present more peripherally in the parasympathetic submandibular ganglia. These bodies were also present in superior cervical ganglia together with non-neurological tissue (submandibular salivary glands). Recent studies also identified these oral biomarkers in submandibular glands.

Keywords: parkinson, *substantia nigra*, lewy bodies, submandibular glands

Introduction
Parkinson's disease (PD) is a degenerative disorder of the central nervous system. Early in the disease, motor symptoms such as shaking, rigidity, slowness of movement, and difficulty with walking are noticed. These symptoms result from the death of cells in the *substantia nigra*. cell death is due to modification of some intracellular proteins into Lewy bodies; resulting in dopamine deficiency. Non-motor symptoms, range from dysphagia, salivary overflow or altered saliva secretion (Dewey *et al*, 2012; Khoo *et al*, 2013; Maass and Reichmann, 2013; Srivanitchapoom *et al*, 2014; Zlotnik *et al*, 2015) [13, 29, 34, 56, 63]. In the advanced stages of the disease, other symptoms such as dementia, depression and anxiety become obvious.

Innervations of submandibular glands and PD pathophysiological pathways
Submandibular glands are innervated by the autonomic nervous system including the parasympathetic innervation provided by the superior salivatory nucleus via the chorda tympani, a branch of the facial nerve, which becomes part of the lingual nerve prior to synapsing on the submandibular ganglion. Increased parasympathetic activity promotes the secretion of saliva. (Ferreira and Hoffman, 2013) [16]. The parasympathetic submandibular ganglia project fibers to the oral mucosa and the sublingual and submandibular salivary glands (Ferreira and Hoffman, 2013) [16].
The sympathetic nervous system regulates submandibular secretions through vasoconstriction of the arteries that supply it. Increased sympathetic activity reduces glandular blood flow, thereby decreasing the volume of fluid in salivary secretions, producing enzyme rich mucous saliva. (Ferreira and Hoffman, 2013) [16].

Biomarkers
Lewy bodies are abnormal aggregates of alpha-synuclein that develop inside nerve cells of the brain in PD. Takeda *et al* (1994) [57] stated that Lewy bodies could be present more peripherally in the parasympathetic submandibular ganglia (Takeda *et al*, 1994) [57]. While, Del *et al*, (2010) [11] proved that, these bodies were also present in superior cervical ganglia together with non-neurological tissue (submandibular salivary glands) (Del *et al*, 2010) [11]. Recent studies also identified these oral biomarkers in submandibular glands (Beach *et al*, 2013; Adler *et al*, 2014) [3, 1].
The mechanisms by which alpha synuclein aggregation are transduced from central nervous tissue to peripheral oral cavity through either parasympathetic or sympathetic innervations are poorly understood (Gibson *et al*, 2000; Aframian *et al*, 2010; Lourenco *et al*, 2010; Farrell *et al*, 2012) [21, 2, 33, 15].
Experiments have provided evidence indicating that alpha-synuclein is able to migrate between neurones through a cell-to-cell spread mechanism (Olanow and Brundin, 2013; Ulusoy *et al*, 2013; Betemps *et al*, 2014) [43, 59, 4]. It also can spread from gastrointestinal tract to brain tissue (Holmqvist *et al*, 2014) [24]. So, one may not deny the possibility that a reverse path of PD pathology spread could also occur towards the oral cavity affecting the submandibular gland (Isaacs *et al*, 2008; Polymenidou and Cleveland, 2011; Uchida *et al*, 2012) [26, 46, 58].

Effects of exercise in PD and potential impact on oral cavity
Fisher *et al* (2013) [17] examined the effect of high-intensity exercise on dopaminergic neurotransmission with early-stage PD. Exercise increases brain-derived neurotrophic factor

(BDNF) levels (Fisher *et al*, 2013; Frazzitta *et al*, 2014; Zoladz *et al*, 2014) [17, 19, 64].

Prior studies had shown a link between serum levels of BDNF and motor impairment in PD (Scalzo *et al*, 2010) [49]. Bos *et al* (2011) [6] demonstrated that serum BDNF levels were lower among cyclists who cycled in traffic-related air pollution than in controlled indoor environments (air-filtered room) (Bos *et al*, 2011) [6]. The study by Bos *et al* (2011) [6] is particularly clinically relevant to the results of the recent study by van der Kolk *et al* (2014) [31] which reported that individuals with PD are able to increase the weekly amount of physical activity (van der Kolk *et al*, 2014) [31]; however, in high air pollution environments, the BDNF enhancing effects on brain plasticity may be minimal.

Whether exercise affects PD symptoms only; or, at the same protect oral cavity from the effects of the disease on submandibular glands, constitutes a core question. Therefore, as exercise leads to increase in norepinephrine levels in brain and blood, one may further examine such changes in submandibular glands and saliva (Matta Mello *et al*, 2013) [38].

Because wild-type alpha-synuclein was shown to regulate dopaminergic neuronal cell apoptosis and presynaptic plasticity in the corticostriatal pathway, investigation of the effects of exercise on alpha-synuclein activity might provide further clues about PD pathogenesis (Watson *et al*, 2009; Yasuda and Mochizuki, 2010) [60, 61].

Assessment of oral cavity biomarkers in responsive to exercise in PD.

The neuroprotective or neurorestorative effects of exercise may be measured in saliva or other oral cavity tissues such as the oral mucosa, dental plaque (Adler *et al*, 2014) [1].

Such measurements of biomarkers expressed or secreted by submandibular glands may be obtained by needle biopsy or aspirate (Adler *et al*, 2014) [1]. Molecular changes in live oral mucosal cells may be measured from biological samples obtained from cell surface scrapping using cytobrushes (Reboiras-Lopez *et al*, 2012) [48]. Dental plaque (supra- or subgingival) may be collected using scalers or brushes to determine the composition and gene expression of the plaque microbiome (Peterson *et al*, 2014; Gomes *et al*, 2015) [44, 22].

Hong *et al* (2010) [25] showed that alpha-synuclein expression in cerebrospinal fluid (both reduced in patients with PD compared to controls) provided high sensitivity for PD diagnosis (Hong *et al*, 2010) [25].

However, such diagnostic power was lost when these markers were measured in saliva in which a trend for lower expression of alpha-synuclein was observed (Devic *et al*, 2011) [12].

Changes that result from short-term exercise need to be distinguished from effects of sustained long-term exercising might need to be interrupted if it constituted a health risk (high risk/benefit ratio) for elderly PD patients who display contraindications to exercise (e.g., cardiovascular disease or advanced dementia).

Also, non-motor symptoms may be present years before the emergence of motor symptoms which are required to establish a definite PD diagnosis, thereby making it difficult to investigate etiological mechanisms in PD (Chen *et al*, 2013) [9].

Overall, because there is a large body of evidence that alpha-synuclein and dopamine pathway perturbations are central to PD pathogenesis, one may evaluate potential relationships candidate biomarkers have with these pathway perturbations. Such relationship could provide some clues as to whether candidate biomarkers have potential to generate a disease biosignature on their own or by means of signal transduction pathways.

Biosignatures may thus be further tested and validated by molecular analyses of oral cavity of human or animal models of exercise and PD. A relatively broad range of candidate biomarkers (proteins and miRNAs) have been characterized in cerebrospinal fluid, blood, saliva, or brain compartments (frontal cortex, *substantia nigra*, and basal ganglia) in live or postmortem PD patients (Brooks and Pavese, 2011; Khoo *et al*, 2012; Sierra *et al*, 2013; Chahine *et al*, 2014; Mollenhauer, 2014) [7, 28, 55, 8, 40]. Some of these molecular markers may be associated with motor symptoms, for example, alpha-synuclein in CSF (Mollenhauer, 2014) [40]. Others might rather be associated with non-motor features of PD (Mollenhauer *et al*, 2014) [41].

For example, a longer splice-variant transcript of SRRM2 was shown to be down regulated in the amygdala of the limbic system which controls fear and anxiety in humans, although it remains to be determined whether such down regulation affects patients with PD in this regard (Martin *et al*, 2009; Shehadeh *et al*, 2010) [36, 54]. it represents candidate proteins involved in PD responsive to exercise as determined by detection in blood, saliva, brain, or other biological compartment.

With the prospect of detection in oral cavity compartment in humans or animal models, all proteins listed in Table 2 may be expressed in saliva, the salivary glands, the oral mucosal epithelium, or the salivary autonomic nervous system. These candidate biomarkers (or their downstream targets) could be further investigated for their association with molecular changes induced within these oral cavity components or with induced changes in microbiota composition. In addition, their neuroprotective or neurotrophic role or relationship with pathophysiological pathways in PD is described. Molecular entities with known/suspected role or potential benefit in PD, not yet investigated in oral tissues or saliva in patients with PD undergoing exercise, may also qualify as valuable candidates.

One may, thus, consider miRNAs responsive to exercise and potentially involved in alpha-synuclein expression, aggregation, or processing by chaperone-mediated autophagy mechanisms (Doxakis, 2010; Liu *et al*, 2010; Goodall *et al*, 2013) [14, 32, 23]. Figure 2 illustrates the intersection between the gene listings presented in Table 1 (i.e., genes involved in neuroplasticity) and Table 2 (i.e., genes involved in response to exercise in oral cavity). Genes from the intersection (BDNF, CAT, DRD2, GDNF, GFAP, GRIA2, NOS2, SOD1, VEGFA) constitute candidate biomarkers (or surrogates) responsive to exercise in PD and involved in molecular pathways that are potentially perturbed by PD disease mechanisms that affect the nervous autonomous system in oral cavity.

In addition to changes affecting molecular entities, PDspecific changes in the oral microbiome can also be anticipated, as exercise was, for example, shown to attenuate polychlorinated

biphenyl-induced changes in the mouse gut microbiome and altered the microbiota composition of rat cecum (Matsumoto *et al*, 2008; Choi *et al*, 2013) [37, 10]. Also, changes in the gut microbiome that are associated with constipation (non-motor symptom) and severity of postural instability and gait difficulty (motor symptoms) have been identified in patients with PD (Scheperjans *et al*, 2015) [50].

Over one hundred known molecular entities (proteins, peptides, miRNAs, metabolites) may be tested as 'relevant' candidate biomarkers for PD, in oral cavity and in response to exercise. Thus, approaches that have been helpful to better characterize the 'gut–brain' relationship in neurological disorders may serve as guidance to conduct oral biomarker discovery in PD.

Conclusion

Here, we propose that exercise-induced neuroplasticity can be transduced from the brain to oral cavity. As a corollary, we suggest that oral biomarkers for PD may be affected in oral cavity in response to exercise. Other studies suggest using these biomarkers in diagnostics protocols.

Over the past decade, a significant number of candidate biomarkers for PD with potential diagnostic value have been described. Much research remains on the effect of exercise on neuroplasticity in PD and a consensus on the type of oral biomarker needs to be validated before applying these biomarkers for determination of the disease state and therapeutic response including exercise. No candidate oral biomarker has yet been demonstrated to provide adequate diagnostic value with regard to disease stratification, onset and progression, or response to drug/treatment, in a large cohort of patients with PD compared to healthy controls or related neurological disease controls. The importance of incorporating exercise, which clearly modulates neuroplasticity, in experimental designs used in the search for PD biomarkers in oral cavity remains underestimated and underinvestigated.

Because alpha-synuclein abnormalities have been characterized in submandibular glands and gut of patients with PD, alteration of the gut or oral microbiota might generate PD-specific biosignatures or peculiar interactions with the microbiome of the digestive tract overall in PD. Investigation of pathophysiological pathways between oral cavity and brain connectivity in PD is thus needed to determine the extent to which molecular or microbiomic composition of oral cavity (saliva, oral mucosa, dental plaque, and gingiva) defines patterns that are associated with the onset or progression of the disease. In this regard, next-generation sequencing metagenomics and metatranscriptomics may prove helpful for investigators to garner further fundamental knowledge of exercise-induced neuroplasticity in PD.

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