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High lithium levels in tobacco may account for reduced incidences of both Parkinson's disease and melanoma in smokers through enhanced β-catenin-mediated activity

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ABSTRACT

Parkinson's disease (PD) patients have higher rates of melanoma and *vice versa*, observations suggesting that the two conditions may share common pathogenic pathways. β-Catenin is a transcriptional cofactor that, when concentrated in the nucleus, upregulates the expression of canonical Wnt target genes, such as Nurr1, many of which are important for neuronal survival. β-Catenin-mediated activity is decreased in sporadic PD as well as in leucine-rich repeat kinase 2 (LRRK2) and β-glucosidase (GBA) mutation cellular models of PD, which is the most common genetic cause of and risk for PD, respectively. In addition, β-catenin expression is significantly decreased in more aggressive and metastatic melanoma. Multiple observational studies have shown smokers to have significantly lower rates of PD as well as melanoma implying that tobacco may contain one or more elements that protect against both conditions. In support, smoker's brains have significantly reduced levels of α-synuclein, a pathological intracellular protein found in PD brain and melanoma cells. Tobacco contains very high lithium levels compared to other plants. Lithium has a broad array of neuroprotective actions, including enhancing autophagy and reducing intracellular α-synuclein levels, and is effective in both neurotoxin and transgenic preclinical PD models. One of lithium's neuroprotective actions is enhancement of β-catenin-mediated activity leading to increased Nurr1 expression through its ability to inhibit glycogen synthase kinase-3 β (GSK-3β). Lithium also has anti-proliferative effects on melanoma cells and the clinical use of lithium is associated with a reduced incidence of melanoma as well as reduced melanoma-associated mortality. This is the first known report hypothesizing that inhaled lithium from smoking may account for the associated reduced rates of both PD and melanoma and that this protection may be mediated, in part, through lithium-induced GSK-3β inhibition and consequent enhanced β-catenin-mediated activity. This hypothesis could be directly tested in clinical trials assessing lithium therapy's ability to affect β-catenin-mediated activity and slow disease progression in patients with PD or melanoma.

Background

Epidemiologic studies have shown cigarette smokers to have a reduced risk of Parkinson's disease (PD) with large prospective cohort studies showing a mean 77% reduced risk [1]. Although reverse causality may be a contributing factor (i.e. preclinical PD causing smoking aversion or smoking cessation) [2]; reduced rates of PD in those exposed to second hand smoke, findings from monozygotic twin studies and historical variations in PD incidence being inversely correlated with variations in smoking behavior suggest that tobacco contains one or more neuroprotective elements that can reduce the incidence of PD [3–7]. Out of the hundreds of compounds in tobacco, nicotine has received the most attention; however, the fact that 1-year of nicotine patch therapy led to worse clinical outcomes than placebo patch therapy in the recent NIC-PD trial makes it unlikely that nicotine therapy can provide disease-modifying benefit in PD [8]. This raises the possibility that there may be other element(s) in tobacco accounting for the strong and consistent PD risk reduction observed in smokers.

Another consistent human epidemiologic finding is the approximate 3-fold increased incidence of melanoma in PD patients [9,10]. Also, having a personal or family history of melanoma; but not colorectal, lung, prostate or breast cancer; is associated with significant increased risks for PD [11,12]. These observations suggest that PD and melanoma share common genetic risks and/or pathogenic molecular pathways. In addition, 86–89% of malignant melanoma and benign melanocytic lesions contain α-synuclein, the pathologic hallmark of PD, while non-melanocytic cutaneous carcinoma and normal skin do not contain α-synuclein, which further supports a common pathogenic etiology

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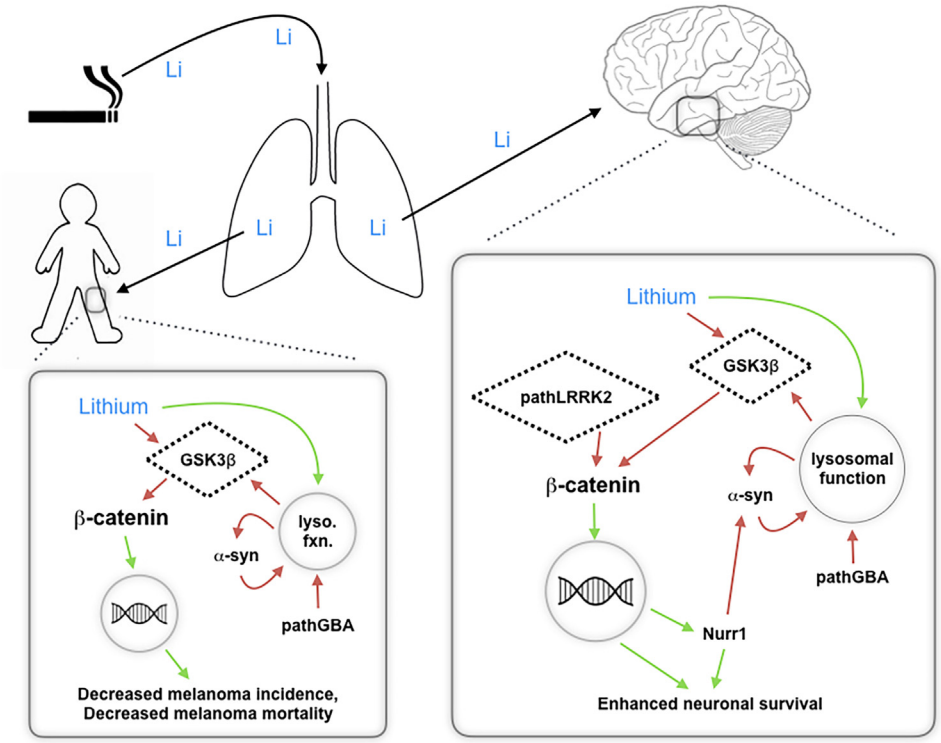

Fig. 1. Hypothesis explaining the reduced rates of Parkinson's disease and melanoma in smokers. *Legend*: Li: lithium, pathLRRK2: Parkinson's disease-causing mutations in leucine-rich repeat kinase 2 gene, pathGBA: neuronopathic mutations in β-glucosidase gene, GSK-3β: glycogen synthase kinase-3β, α-syn: α-synuclein, Nurr1: orphan nuclear receptor Nurr1, lyso. fxn.: lysosomal function. Green/red arrows depict actions that increase/decrease activity or protein levels.

between PD and melanoma [13]. Interestingly, large prospective studies show male smokers to have a significant 37–47% decreased risk of developing melanoma with up to a 68% reduced risk associated with smoking > 15 cigarettes per day [14,15]. Therefore, tobacco may contain one or more elements that targets a pathogenic pathway common to PD and melanoma leading to reduced incidences of both conditions in smokers.

As in PD, nicotine was proposed as an element in tobacco potentially providing protection against incident melanoma, although nicotine has never been shown to be cytotoxic to or to prevent proliferation of melanoma cells [14]. On the contrary, nicotine has been shown to stimulate the proliferation of lung and pancreatic cancer cells [16]. Smoking-induced downregulation of Notch pathway gene expression was proposed to account for reduced melanoma incidence in smokers [14,17]. However, cells expressing α-synuclein were shown to have reduced Notch levels and neuronal survival, the latter of which was reversed by overexpression of the Notch intracellular domain [18]. These data imply that smoking would recapitulate, not interfere with, pathophysiology implicated in α-synuclein-mediated neuronal toxicity. Several theories have been proposed regarding shared pathophysiology between PD and melanoma including alterations in melanin synthesis, tyrosine metabolism, α-synuclein expression and autophagy as well as several genetic variations [9,11,19–21]. However, none of these theories has incorporated how smoking may influence these pathways and lead to the reduced associated incidences of both PD and melanoma.

Hypothesis: Inhaled lithium accounts for the reduced risks of PD and melanoma in smokers by enhancing β-catenin-mediated activity.

In 1980, high levels of lithium were reported in tobacco from India: levels about 20-fold higher than any plant or animal food tested [22]. Our group recently reported that tobacco from the popular western cigarette brands, *Camel* and *Marlboro*, has as high or higher lithium levels than Indian tobacco [23]. Although it is not known how much of the inhaled lithium is systemically absorbed from cigarette smoking, we estimated that a pack-per-day smoker may absorb about 169–338 μg of lithium/day. For perspective, a daily oral lithium dose of 300 μg for 15 months was shown to significantly slow cognitive decline in a randomized controlled trial among 110 patients with early Alzheimer's disease [24]. Furthermore, a large Danish epidemiologic study recently found significantly reduced rates of dementia and Alzheimer's disease in municipalities with the highest levels of lithium in the drinking water [25]. Therefore, it is plausible that daily microdose lithium exposures in pack-per-day smokers could potentially prevent or slow neurodegenerative disease. Use of prescription lithium carbonate has also been associated with significantly reduced rates of dementia and Alzheimer's disease [26–28]. It was also proposed that the current lack of epidemiologic data associating prescription lithium use with a reduced incidence of PD may be due to the common occurrence of lithium-induced hand tremors being misdiagnosed as PD [29] when dosed for mood stabilization (about 600–2000 mg/day) [23]. Because lithium-induced hand tremors are dose related, such tremors would not be expected to occur from daily exposure to 169–338 μg of lithium in pack-per-day cigarette smokers and, therefore, not obfuscate its potential ability to reduce incident PD in this population.

Lithium carbonate was FDA-approved in 1970 for treating bipolar disorder, although its mechanism of action has never been clearly understood for this indication. In addition to its symptomatic benefits for bipolar disorder, lithium also has several neuroprotective actions including decreasing the aggregation and phosphorylation of α-synuclein and tau; enhancing autophagy and reducing oxidative stress, inflammation, microglia activation and apoptosis [30–34]. Lithium has also demonstrated neuroprotective effects in several animal models of PD including neurotoxin and transgenic models [35–37]. There is substantial evidence supporting prion-like intraneuronal accumulation and interneuronal spread of toxic oligomeric α-synuclein as primary mediators of progressive neuronal demise in PD [38]. The autophagy-lysosomal pathway is a key route for degradation of intracellular aggregate-prone proteins such as α-synuclein; however, α-synuclein itself leads to impaired autophagy and lysosomal function [39], which then impairs the cell's ability to clear α-synuclein (Fig. 1). Therefore, therapies that can increase the clearance and/or reduce the formation of α-synuclein may break this vicious cycle of α-synuclein accumulation and neuronal demise and potentially offer disease-modifying effects in PD.

Lithium can enhance autophagy and directly reduce α-synuclein

levels via inhibition of inositol monophosphate [33]. In addition to stimulating autophagic clearance of intraneuronal α-synuclein, lithium also enhances β-catenin-mediated activity leading to increased expression of the orphan nuclear receptor Nurr1, which can decrease the formation of α-synuclein (Fig. 1) [40,41]. In support, post-mortem brains of heavy smokers have significantly reduced α-synuclein deposition compared to non-smokers [42]. Inhaled lithium from smoking could account for this finding through enhanced autophagy via inositol monophosphatase inhibition and reduced expression of α-synuclein via enhanced β-catenin-mediated activity. β-Catenin is a transcriptional cofactor that, when concentrated in the nucleus, upregulates the expression of canonical Wnt (Wingless/Integration) target genes, such as Nurr1, many of which regulate neuronal survival, axonal outgrowth and synaptic integrity [43]. Nurr1 regulates the expression of several genes essential for dopaminergic neuronal differentiation, maintenance and survival [44]. Nurr1 levels are significantly reduced by about 65% in PD substantia nigra neurons expressing α-synuclein and 61% in PD peripheral blood mononuclear cells (PBMCs) compared to healthy controls [45,46]. Several Nurr1 gene mutations have also been identified as genetic risks for both familial and sporadic PD [44]. Nurr1 expression in human SN decreases with increasing age, the major risk factor for PD, and is highly correlated with expression of tyrosine hydroxylase, the rate-limiting step in dopamine production [47].

Besides its specific influence on Nurr1 expression, decreased β-catenin-mediated activity has also been implicated in the pathophysiology of sporadic PD [43] as well as leucine-rich repeat kinase 2 gene mutations (pathLRRK2) [48], the most common genetic cause of PD, and neuronopathic mutations in the β-glucosidase gene (pathGBA) [49], the most common monoallelic genetic risk for PD. PathLRRK2 causes a late-onset parkinsonism clinically indistinguishable from sporadic PD and with very similar pathology [48]. As a result, there has been much interest in identifying pathLRRK2 physiology to identify potential PD disease-modifying therapeutic targets.

Strong evidence supporting reduced β-catenin-mediated activity in pathLRRK2 PD pathophysiology stems from the finding that β-catenin-mediated activity is significantly decreased in several pathLRRK2 cellular models but is significantly increased in cells carrying the PD protective LRRK2 mutation, R1398H, compared to wild-type LRRK2 [48]. β-Catenin is regulated, in part, via phosphorylation by glycogen synthase kinase-3β (GSK-3β) leading to its further ubiquitination and eventual proteasomal degradation [43]. Use of GSK-3β inhibitors, such as lithium, decreases β-catenin phosphorylation and increases β-catenin-mediated transcription activity, such as Nurr1 expression (Fig. 1) [40]. As noted, monoallelic pathGBA, which codes for the lysosomal enzyme β-glucocerebrosidase, is the most common genetic risk for sporadic PD and, like pathLRRK2, likely produces pathophysiology clinically relevant for sporadic PD. Induced pluripotent stem cells with pathGBA show impaired lysosomal function leading to increased levels of activated GSK-3β, reduced canonical Wnt/β-catenin signaling, impaired ability to differentiate into dopaminergic cells and reduced survival (Fig. 1). These pathGBA cellular findings were all reversed with activation of the canonical Wnt/β-catenin pathway or with use of recombinant β-glucocerebrosidase [49]. Proper lysosomal activity is believed to regulate β-catenin levels through lysosomal sequestration of activated GSK-3β leading to reduced cytosolic β-catenin phosphorylation and degradation [49]. Thus, lysosomal dysfunction can contribute to neuronal demise in PD by directly impairing the degradation of toxic α-synuclein species as well as by reducing β-catenin levels and β-catenin-mediated activity, such as Nurr1 expression, which are important for neuronal survival (Fig. 1).

β-Catenin-mediated activity is also implicated in melanoma pathophysiology. β-Catenin expression is significantly decreased in more aggressive and metastatic melanoma compared to less aggressive melanoma and non-malignant melanocytic naevi [50]. Transcriptional profiling has revealed that activation of the Wnt/β-catenin pathway leads to upregulation of several genes that are lost in aggressive melanomas compared to normal melanocytes [50]. Patient survival is also positively correlated with melanoma nuclear β-catenin levels. Furthermore, use of a GSK-3β inhibitor was shown to increase β-catenin-mediated activity and cell death in melanoma cells [51] and lithium was also shown to inhibit melanoma cell proliferation, *in vitro* [50]. Finally, a large epidemiologic study showed clinical use of lithium to be associated with a significantly reduced incidence of melanoma as well as reduced melanoma-associated mortality (Fig. 1) [52]. It should be noted, however, that the vast majority of patients taking lithium would be expected to have bipolar disorder, which may have introduced a bias in this study's results, although no link between bipolar disorder and melanoma has been previously reported. Also, the lithium dosages used to treat bipolar disorder are several orders of magnitude higher than those to which smokers may be exposed, which may be relevant in terms of melanoma prevention.

A single observational study showed patients with Gaucher's disease, an inherited lysosomal storage disease caused by biallelic pathGBA, to have over 3-fold the risk of developing melanoma compared to people without Gaucher's [53]. This observation suggests that lysosomal dysfunction may also contribute to melanoma pathophysiology, similar to PD, leading to the intracellular α-synuclein accumulation seen in both conditions (Fig. 1) [13,39].

Although PD is associated with higher rates of melanoma, PD is also associated with significantly lower rates of several non-skin cancers; including colorectal, hematologic, prostate and lung cancers; and a lower risk of dying from cancer [19,54]. These disparities may be related to β-catenin-mediated activity differentially influencing the incidence of various cancers. For example, reduced β-catenin-mediated activity has been implicated in melanoma etiology while increased β-catenin-mediated activity, from constitutively activated Wnt/β-catenin signaling, has been implicated in the etiology of many other cancers especially colorectal cancer [55]. Thus, reduced β-catenin-mediated activity in PD may partially explain both the associated increased incidence in melanoma and decreased incidences in other cancers. Use of prescription lithium has not been associated with increased incidences of any cancers [56].

Conclusions

This is the first known report hypothesizing that high lithium levels in tobacco may account for the reduced rates of both PD and melanoma in smokers and that these observations may be mediated through lithium-induced GSK-3β inhibition and consequent enhanced β-catenin-mediated activity. Because of the consistent link found in observational studies between PD and melanoma and their shared pathophysiology [9,11,13,43,48–50,53], therapies known to inhibit GSK-3β and/or enhance β-catenin-mediated activity should be considered for investigation in PD and melanoma clinical trials. In particular, clinical investigation of low-dose lithium therapy in PD is merited considering lithium's significant neuroprotective effects in preclinical PD models and abilities to inhibit GSK-3β and enhance β-catenin-mediated activity, actions implicated as beneficial based on genetic contributions to PD [35–37,40,48,49]. Also, low-dose lithium therapy appears to be well tolerated clinically in PD and may provide symptomatic benefit [57]. The possibility that inhaled lithium from smoking could account for the 77% reduced risk of PD in smokers provides additional support to investigate lithium's potential disease-modifying effects in PD as was recently performed for nicotine therapy based on similar justifications [8]. These data also support exploring GSK-3β and β-catenin-mediated activity, perhaps in PBMCs, as potential therapeutic biomarkers of disease-modifying therapies in PD and melanoma.

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Declaration of Competing Interest

Thomas Guttuso, Jr., is also President of e3 Pharmaceuticals, Inc.

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