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Letter to the Editor

Could high lithium levels in tobacco contribute to reduced risk of Parkinson's disease in smokers?

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Dear Editor

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]. As a result, many have theorized that tobacco may contain one or more neuroprotective elements that could reduce the incidence and slow the progression of PD.

Out of the hundreds of compounds in tobacco, nicotine has received the most attention. The NIC-PD trial was the largest randomized, double blind, placebo controlled, nicotine PD clinical trial to date. This trial found no significant intergroup difference for the study's primary endpoint and, surprisingly, a significantly worse outcome for those randomized to the nicotine patch for the secondary endpoint [2]. Based on these results, it appears unlikely that nicotine therapy can offer benefit for PD, which raises the possibility that there may be other element(s) in tobacco accounting for the strong and consistent PD risk reduction observed in smokers.

In 1980, high levels of lithium were reported in tobacco from India: levels about 20-fold higher than any food tested [3]. Lithium has a wide range of neuroprotective actions including decreasing the aggregation and phosphorylation of alpha-synuclein and tau; enhancement of autophagy and reduction of oxidative stress, inflammation, microglia activation and apoptosis and has demonstrated neuroprotective actions in several animal models of PD. [4–6] In addition, a daily microdose of lithium was shown to significantly slow cognitive decline in early Alzheimer's disease patients [7]. Therefore, it is biologically plausible that daily exposure to microdose amounts of lithium from cigarette smoking could impart neuroprotective/disease-modifying effects in neurodegenerative disease.

As almost all of the aforementioned epidemiologic studies were performed in western countries, we assessed lithium levels in tobacco from popular brands of western cigarettes to compare with that previously reported in Indian tobacco. Subsequently, we assessed lithium levels in varieties of whole-leaf tobacco to explore the disparate lithium levels we found in different brands of western cigarettes.

1. Methods

Tobacco samples from five brands of western cigarettes and four types of whole-leaf tobacco (Table 1) were analyzed for lithium content using inductively coupled plasma optical emission spectrometry (Optima 2000DV, Perkin Elmer). Cigarettes and whole-leaf tobacco were purchased from a local convenience store and *Leaf Only*, Middletown, CT, respectively. Samples of tobacco were accurately weighed and digested overnight in 69% trace metal analysis grade nitric acid at room temperature. After digestion, the suspension was centrifuged and filtered. A 1 ml aliquot of the filtrate was diluted to 10 ml with 2% nitric acid prior to analysis similar to previously published methods [8].

Argon, compressed air and nitrogen were used as the plasma gas, shear gas and purge gas, respectively. Certified lithium standards (Perkin Elmer) were used for instrument calibration. Yttrium (Perkin Elmer) was added to all blank, standard and sample solutions as an internal standard. All solutions were analyzed in triplicate using the 670.8 nm emission line for lithium and the 371.0 nm line for yttrium.

2. Results

3. Discussion

This is the first ever report of lithium levels in non-Indian tobacco. We found lithium levels in popular brands of western cigarettes to be as high or higher than that previously reported in Indian tobacco [3], with the exception of *American Spirit* (blue regular filter) brand cigarettes (Table 1). Besides tobacco, the plant or animal products previously reported with the highest lithium levels were black-eyed peas (0.65 μg/g) and black beans (0.35 μg/g) [3,8]. Therefore, tobacco contains about 20-100× the amount of lithium as the next highest plant reported.

In order to explore why *American Spirit* tobacco had lithium levels approximately an order of magnitude less than *Camel* or *Marlboro* tobacco, *Santa Fe Natural Tobacco Company* (manufacturers of *American Spirit* cigarettes) was contacted. Company literature cited *American Spirit* cigarettes to contain approximately 90% flue-cured Virginian tobacco and a 10% blend of US-grown burley and Turkish oriental tobaccos (personal communication). *R.J. Reynolds* and *Philip Morris* (the manufacturers of *Camel* and *Marlboro* cigarettes, respectively) did not

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Table 1
Mean lithium levels in cigarette and whole-leaf (WL) tobacco.

Tobacco source	Lithium concentration (μg/g)
Camel Blue	25.0
Camel Turkish Gold	15.0
Marlboro Red	15.1
Marlboro Gold	12.6
American Spirit (blue regular filter)	2.6
Indian Tobacco [3]	12.0
Izmir Turkish Oriental WL Tobacco	65.5
Samsun Turkish Oriental WL Tobacco	53.1
Brightleaf Virginia WL Tobacco	11.1
American Virginia WL Tobacco	0.0

provide such information upon inquiry but *Camel* cigarette containers state that their tobacco is a "Turkish & Domestic Blend". Therefore, we hypothesize that it is the low amount of Turkish tobacco in *American Spirit* cigarettes that accounts for the relatively low lithium levels in its tobacco (Table 1).

Because the lithium ion is the smallest alkali metal and is known to rapidly pass through sodium channels, it would appear likely that most of inhaled lithium from smoking cigarettes would be systemically absorbed through the lungs; however, this has never been formally assessed to our knowledge. For illustration purposes, if one assumes that 50–100% of the inhaled lithium from cigarette smoking is absorbed through the lungs, a pack-per-day smoker of *Camel* or *Marlboro* cigarettes would absorb about 169-338 μg of lithium/day considering 20 cigarettes/pack, about 1 g of tobacco/cigarette and a mean tobacco lithium level of 16.9 μg/g in these brands. As previously mentioned, a daily oral lithium dose of 300 μg for 15 months was shown to significantly slow cognitive decline in early Alzheimer's disease in a randomized, double blind, placebo controlled trial [7]. Therefore, it is plausible that daily microdose lithium exposures in pack-per-day smokers could potentially prevent or slow neurodegenerative disease.

Although observational studies have shown up to a 62% reduced rate of dementia in Bipolar disease patients receiving lithium therapy compared to Bipolar disease patients receiving anticonvulsant, antipsychotic or antidepressant therapy [9]; reduced rates of PD in Bipolar disease patients receiving lithium therapy has not been reported. One potential explanation for this is lithium-induced hand tremors being misdiagnosed as PD when dosed for mood stabilization (about 600–2000 mg/day). In support, older patients receiving lithium therapy are more likely to receive PD medications than those receiving antidepressant therapy, which was proposed to be due to inappropriate treatment of lithium-induced hand action tremors [10]. As lithium-induced tremors are dose related, hand 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.

In conclusion, we have found high levels of lithium in popular brands of western cigarettes and hypothesize that inhaled lithium from smoking may partially account for the strong and consistent reduced incidence of PD in smokers. To our knowledge, this is the first report proposing this theory. Although inhaled lithium from smoking may lead to a reduced risk for PD, the health dangers of smoking clearly outweigh any such potential benefit. Considering the large body of preclinical and clinical data supporting lithium's neuroprotective and potential disease-modifying actions, which is more comprehensive than nicotine's, further clinical research on lithium therapy in PD should be considered.

Declarations of interest

Thomas Guttuso, Jr., MD is also President and CEO of e3 Pharmaceuticals, Inc., which is seeking to develop a lithium formulation for treating Parkinson's disease.

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