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OLFACTORY DYSFUNCTION IN PARKINSON'S DISEASE: POSITIVE EFFECT OF CIGARETTE SMOKING

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Abstract

Background—There is compelling evidence from over 60 epidemiological studies that smoking significantly reduces the risk of Parkinson's disease (PD). In general, those who currently smoke cigarettes, as well as those with a past history of such smoking, have a reduced risk of PD compared to those who have never smoked. Recently it has been suggested that a cardinal non-motor sensory symptom of PD, olfactory dysfunction, may be less severe in PD patients who smoke than in PD patients who do not, in contrast to the negative effect of smoking on olfaction described in the general population.

Methods—We evaluated University of Pennsylvania Smell Identification Test (UPSIT) scores from 323 Parkinson's patients and 323 controls closely matched individually on age, sex, and smoking history (never, past, current).

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Results—The patients exhibited much lower UPSIT scores than did the controls ($P<0.0001$). The relative decline in dysfunction of the current PD smokers was less than that of the never- and past-PD smokers (respective P s=0.0005 & 0.0019). The female PD patients outperformed their male counterparts by a larger margin than did the female controls (3.66 vs. 1.07 UPSIT points; respective P s < 0.0001 & 0.06). Age-related declines in UPSIT scores were generally present ($P < 0.0001$). No association between the olfactory measure and smoking dose, as indexed by pack years, was evident.

Conclusions—PD patients who currently smoke do not exhibit the smoking-related decline in olfaction observed in non-PD control subjects who currently smoke. The physiologic basis of this phenomenon is yet to be defined.

Keywords

Parkinson's disease; olfaction; psychophysics; UPSIT; cigarette smoking; L-DOPA

Introduction

Prospective and retrospective epidemiological studies have reported a significant inverse association between smoking and Parkinson's disease (PD).^{1–4} PD risk is lowest among subjects with the longest duration of smoking, the greatest lifetime dose of smoking, the most cigarettes smoked per day, and, in past smokers, the fewest years since quitting.

Among the most salient sensory signs of PD is olfactory dysfunction -- dysfunction that adversely influences safety, food flavor, and quality of life.^{5–8} In some cases, the deficit occurs years before the onset of the cardinal motor symptoms.⁹ PD-related pathology likely begins within the olfactory bulbs, the anterior olfactory nucleus, and the dorsal motor nucleus of the vagal glossopharyngeal nerve complex, only later affecting the substantia nigra.¹⁰

In light of such findings, does smoking also influence the magnitude of PD-related olfactory dysfunction? Two relative small studies have addressed this question. Lucassen et al.¹¹ found higher scores on the University of Pennsylvania Smell Identification Test (UPSIT) in 22 smokers with PD than in 54 PD patients who had never smoked ($p<0.02$). Moccia et al.¹² found no UPSIT differences between 10 PD current smokers and 58 PD never-smokers. However, 10 currently smoking controls underperformed 51 never-smoking controls, suggesting that smoking protected against olfactory dysfunction in their PD cohort.

We sought to more definitively establish whether present or past smoking alters the olfactory dysfunction of PD by using data from a large number of PD patients and healthy controls matched on the basis of sex, age, and smoking history.

Methods

Subjects

Data from 323 PD patients and 323 matched normal controls were obtained from previous studies (e.g.,^{13–16}), from the Movement Disorders Center at Pennsylvania Hospital,

Philadelphia, and from the Parkinson's Disease Research, Education, and Clinical Center of the Philadelphia VA Medical Center. Once the subject numbers noted Table 1 had been reached, data recruitment was stopped for the never- and past-smoking groups. All current smoking PD patients that could be identified were included in the study.

Patients met the Gelb et al. criteria for possible PD.¹⁷ Medication usage data were available for 144 patients, 24 of whom were not taking any PD-related medications. Hoehn & Yahr (H&Y) scores were available for 224 patients. Pack years were available for all but three PD patients. The mean (SD) time elapsed between smoking cessation and test administration did not differ between the past-smoking PD patients and controls [18.4 years (10.1) vs. 19.1 years (13.2); $P=0.92$]. Of the 323 PD patients, 279 were perfectly matched with a control on the basis of age, sex, and smoking status (never, past, current). The remaining 44 were exactly matched to controls on the basis of sex and smoking status; they differed from their individually matched controls in age by no more than a year. Each subject had provided informed written consent and subject participation was approved by the respective institutional human subjects' review boards.

Olfactory Testing

The UPSIT had been administered to all participants.¹⁸ This highly reliable test (test-retest $r>0.90$)¹⁹ correlates strongly with most other nominally disparate olfactory tests, including detection threshold tests.^{18;20} This test is sensitive to sex and changes in olfactory function related to age and many diseases, including Alzheimer's, Parkinson's, and myasthenia gravis.^{6;8;18;21–25}

Statistical Analyses

UPSIT scores were subjected to analysis of covariance (ANCOVA; age = covariate) with the between subjects factor of sex and the within subjects factor of subject group (PD patients, matched controls). Analyses of variance (ANOVAs) assessed interaction effects. Control minus PD UPSIT scores were similarly analyzed to assess the relative PD-related declines in olfactory function. Partial correlations controlling for age were computed among selected measures.

Results

The mean (95% CI) UPSIT scores are presented in Figure 1. Overall, the patients exhibited much lower scores than did the controls [$F(1,316)=20.50$, $P<0.0001$]. The age covariate was significant [$F(1,315)=41.96$, $P<0.00001$], reflecting the well-known age-related decline in UPSIT scores. Significant interactions between subject group (PD, controls) and both sex [$F(1,316)=7.35$, $P=0.007$] and smoking group [$F(2,316)=7.05$, $P<0.001$] were present. The female PD patients outperformed their male counterparts by an average of 3.66 UPSIT points (22.54 vs. 18.88; $P<0.0001$), as compared to the female controls, who outperformed their male counterparts by an average of 1.07 UPSIT points (34.77 vs. 33.70; $P=0.054$). While the UPSIT scores of both the never and past smoking PD groups differed significantly from their respective matched control groups ($p<0.0001$), this was not the case for the current smokers ($p=0.59$). Although no difference in the control minus PD olfactory deficit

was present between PD past smokers and PD never smokers ($P=0.79$), that of the PD current smokers [8.48 (9.83)] was less than that of the PD never smokers [14.85 (9.92)] ($P=0.0005$) and the past PD smokers [14.32 (9.80)] ($P=0.0019$).

No significant associations were present between pack years and either the UPSIT scores or the control minus PD UPSIT difference scores in the current or past smoking PD subjects. Among past smokers, the time elapsed since smoking cessation also did not correlate with these measures, and no significant difference in PD-related olfactory dysfunction was found between the patients on and off PD-related medications. No meaningful correlation was observed between UPSIT deficits and H&Y scores.

Discussion

The present study found that, *relative to matched controls*, olfactory function was less attenuated in current cigarette smokers with PD than in past or never smokers with PD. It should be emphasized, however, that this effect was due, in part, to the poorer performance of the currently smoking non-PD controls, contributing to the smaller difference in relative test scores (Figure 1). Nonetheless, the PD patients who currently smoked did not exhibit the smoking-related decline in function observed in the non-PD controls. This finding accords well with the earlier observations of Lucassen et al.¹¹ and Moccia et al.¹²

While it is conceivable that PD patients who continue to smoke have less advanced disease, evidence that disease stage influences UPSIT scores in a meaningful manner is weak or generally lacking.^{15;26} Interestingly, olfactory dysfunction secondary to exposure to some airborne toxins is less in smokers than in non-smokers, suggesting that smoking may protect the olfactory system from xenobiotic damage.^{27;28} Such protection could reflect nicotine's influences on the cholinergic system. Enhancement of cholinergic function in animals, humans, and animal models of PD facilitates odor detection performance^{29–31} and damage to this system can alter the ability to smell.³² The cholinergic system is associated with olfactory dysfunction in a number of neurodegenerative diseases³² and nicotine from cigarette smoke directly stimulates and up-regulates pre-synaptic nicotine receptors within basal forebrain regions associated with olfactory processing.³³ Nicotine increases blood flow within the olfactory bulb,³⁴ counteracts free radical formation induced by olfactory bulb damage,³⁵ and, in a mouse model of Alzheimer's disease, reduces beta-amyloidosis within the olfactory tract.³⁶ Nicotine likely influences the delicate balance between CNS immune system quiescence and activation.³⁷ Interestingly, nicotine directly activates olfactory receptor neurons via cAMP-mediated canonical olfactory receptor pathways rather than through nicotinic cholinergic receptors.³⁸ Whether such activation promotes maintenance of olfactory function is unknown. The reason why the influences of nicotine are apparent in PD patients, but not in controls, conceivably reflects enhancement of function of a damaged but not intact olfactory epithelium. While PD-related improvement in UPSIT scores may relate to cholinergic influences on non-olfactory elements involved an odor identification task, such as attention or word finding,³⁹ such effects would have to be more accentuated in PD than in healthy controls to produce the current findings.

The major strengths of our study are the large cohort of PD patients and controls individually matched on age, sex, and smoking histories and the use of a highly reliable and well-validated olfactory test. Limitations include the relatively small sample size of the current smoking groups and the lack of complete details regarding medication use (e.g., cholinergic agonists) and smoking behavior (e.g., time since smoking cessation and type of cigarettes smoked).

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Figure 1.

Table 1

Subject demographics.

Subject Group	Smoking Status	Sex	N	Mean Age (SD)	Number with H&Y Score	Mean H&Y Score (SD)	Number taking PD-related Medications
<i>PD</i>	<i>Never</i>	M	111	62.9 (10.6)	87	2.2 (0.7)	39
		F	39	66.6 (8.2)	10	2.3 (1.1)	39
	<i>Past</i>	M	111	67.1 (9.8)	90	2.4 (0.8)	35
		F	39	64.1 (9.4)	25	2.3 (0.9)	23
	<i>Current</i>	M	17	58.8 (11.3)	10	2.4 (0.7)	5
		F	6	69.0 (6.9)	2	3.0 (0.0)	3
<i>Control</i>	<i>Never</i>	M	111	62.8 (10.6)	NA	NA	NA
		F	39	66.7 (8.3)	NA	NA	NA
	<i>Past</i>	M	111	67.0 (9.8)	NA	NA	NA
		F	39	63.7 (9.1)	NA	NA	NA
	<i>Current</i>	M	17	58.7 (11.4)	NA	NA	NA
		F	6	68.8 (6.7)	NA	NA	NA