Lack of Major Olfactory Dysfunction in MPTP-Induced Parkinsonism

Richard L. Doty, PhD,* Anu Singh, MS,† James Tetrud, MD,‡ and J. William Langston, MD†

The olfactory function of 6 patients whose parkinsonism was the result of intravenous administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was compared to that of 12 age-matched patients with idiopathic Parkinson's disease (PD) and 10 age-matched normal control subjects. Unlike their PD counterparts, the olfactory test scores of patients with MPTP-induced parkinsonism did not differ significantly from those of control subjects. These findings suggest that MPTP-induced parkinsonism, unlike idiopathic PD, is unaccompanied, on average, by major alterations in the ability to smell.


Data on Age, Gender, and Smoking Habit for the Three Study Groups

<table>
<thead>
<tr>
<th></th>
<th>MPTP Subjects (n = 6)</th>
<th>PD Subjects (n = 13)</th>
<th>Normal Control Subjects (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD) (yr)</td>
<td>38.83 (6.59)</td>
<td>39.08 (4.75)</td>
<td>38.20 (7.33)</td>
</tr>
<tr>
<td>Male-female ratio</td>
<td>2:4</td>
<td>9:4</td>
<td>4:6</td>
</tr>
<tr>
<td>Proportion of current, previous, and never cigarette smokers</td>
<td>5:0:1</td>
<td>1:5:7</td>
<td>4:2:4</td>
</tr>
<tr>
<td>Mean Hoehn and Yahr stage (SD)‡</td>
<td>3.50 (1.38)</td>
<td>1.31 (0.48)</td>
<td></td>
</tr>
</tbody>
</table>

‡Hoehn and Yahr disease severity rated from 1 to 5.

PD = idiopathic Parkinson's disease; MPTP = parkinsonism induced by intravenous injection of drug contaminated by MPTP; SD = standard deviation.

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Deficits in the ability to detect and identify odors are present in the majority of patients with idiopathic Parkinson's disease (PD) at an age when olfactory dysfunction from other causes is unlikely [1-6]. These perceptual alterations are (1) bilateral [4], (2) stable over time [2], (3) present very early in the disease process [4, 5], (4) independent of antiparkinsonian medications [2-5], and (5) unrelated to disease stage and a number of measures of cognitive and motor dysfunction [2-6]. Although the perceptual deficits are frequently profound, most patients with PD are unaware of their disorder before formal olfactory testing [2, 4].

To date, the olfactory function of patients with other forms of parkinsonism has received little study. For this reason, we administered tests of both odor identification and detection to individuals whose parkinsonism was the result of the intravenous administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and compared the resulting test scores to those of age-matched patients with PD and normal control subjects. We hypothesized that if PD is due to an environmental toxin that enters the body via the olfactory neuroepithelium, individuals with MPTP-induced parkinsonism should have normal olfactory function since their toxic exposure occurred via an intravenous route.

Methods and Materials

Subjects

Six patients whose moderate to severe parkinsonism was directly linked to intravenous MPTP exposure served as subjects [7, 8], along with 13 age-matched patients with PD and 10 control subjects (Table). Five of the PD patients and all of the normal control subjects were tested at the University of Pennsylvania Smell and Taste Center; the patients with MPTP-induced parkinsonism and the remainder of the PD patients were tested at the California Parkinson's Foundation. All subjects were free from nasal obstruction and could sniff adequately and respond verbally to the questions of the examiner without difficulty.

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Assessment of Olfactory Function

The participants were administered the 40-odorant University of Pennsylvania Smell Identification Test (UPSIT), a reliable standardized test of odor identification that is sensitive to a wide range of olfactory deficits [2, 9]. In addition, they were administered a modified single staircase odor detection threshold test using the rose-like odorant phenyl ethyl alcohol (PEA) dissolved in United States Pharmacopeia (USP) grade mineral oil [10], as well as the Picture Identification Test (PIT). The latter test controls for the possibility that abnormal responses on the olfactory tests resulted from cognitive, rather than olfactory, deficits [2, 3].

Results

The mean (± standard error of mean [SEM]) UPSIT and PEA threshold test scores of the three study groups are presented in the Figure. Despite the more advanced parkinsonism and the higher proportion of cigarette smokers in the group with MPTP-induced parkinsonism than in the PD group (see Table), the former group performed significantly better than the latter group on both types of olfactory tests (p < 0.001). Although, on average, the control group outperformed the group with MPTP-induced parkinsonism on both tests (see Fig), these differences were not statistically significant and a larger sample size is needed to ascertain whether this difference is in fact real. As noted in earlier work [2-4], both the UPSIT and the PEA threshold test scores of the PD group were markedly inferior to those of the normal control subjects.

Both the PD and MPTP-induced parkinsonism subjects scored normally on the PIT (respective means [SEM] = 40 [0] and 38 [0.89]), suggesting that nonolfactory cognitive factors did not confound the test performance of either group in any meaningful manner.

Discussion

Olfactory receptor cells are directly exposed to the external environment and project through the cribriform plate to the olfactory bulb, serving as a conduit from

University of Pennsylvania Smell Identification Test (UPSIT) and phenyl ethyl alcohol (PEA) detection threshold test scores for group F (df) and p values were as follows for the UPSIT and threshold measures, respectively: F (2,24) = 6.04, p = 0.008; F (2,24) = 16.47, p < 0.0001. Orthogonal contrasts among the groups were as follows: UPSIT—control versus PD F (1,24) = 10.79, p = 0.003; control versus MPTP-P F (1,24) = 0.09, p = 0.76; PD versus MPTP-P F (1,24) = 5.82, p = 0.024. Threshold—control versus PD F (1,24) = 31.41, p < 0.0001; control versus MPTP-P F (1,24) = 1.33, p = 0.26; PD versus MPTP-P F (1,24) = 12.15, p < 0.002.
the nose to the brain for a number of viruses [11–13], chemicals [14, 15], and metals [16]. For example, 1-methyl-4-phenylpyridinium (MPP+), the toxic metabolite of MPTP that does not readily cross the blood-brain barrier, is transported into the rat olfactory bulb following its infusion into the nasal cavity [17]. Such observations are in accord with the theory that PD might be caused by an environmental neurotoxicant that gains entry to the brain via the olfactory receptor neurons and that the olfactory deficits of this disease reflect damage associated with the path of distribution of the offending agent. There are precedents for this concept. For example, Howe and Bodian [18] demonstrated that the site of entry of the poliomyelitis virus determines its central nervous system (CNS) tropism; only the olfactory bulb and septal nuclei were selectively involved after intranasal inoculation. Similarly, Anderson and Field [11] showed that intranasal inoculation of the herpes simplex virus type 1 (HSV1) involved the olfactory bulb, piriform cortex, and hippocampus, as well as selected areas in the brainstem. These regions were spared when the virus was introduced intravenously or into the brainstem.

Thus, one of the implications of the olfactory vector theory is that the olfactory system should be less affected if exposure to the neurotoxicant occurred via a nonolfactory route. As our test of this hypothesis, we studied a well-defined cohort of individuals who developed their parkinsonism after exposure to the neurotoxicant MPTP via the intravenous, rather than the olfactory, route. The results of this study are in accord with this theory in that we failed to find any significant differences in olfactory function between control subjects and patients with MPTP-induced parkinsonism. Patients with early-onset PD, on the other hand, scored significantly lower on both tests used to evaluate olfaction than did control subjects.

While the present findings are compatible with the olfactory vector theory of PD, as described above, it should be pointed out that there are other potential explanations for our findings. For example, the olfactory dysfunction in PD might simply be due to the degenerative process itself, including retrograde degeneration into the olfactory bulb and epithelium. If so, the lack of an olfactory deficit in MPTP-induced parkinsonism could reflect either the lack of an analogous progressive disease process or a lower susceptibility of the olfactory pathways to damage from circulating MPTP and/or its neurotoxic metabolites. In the rhesus monkey, one report suggests that MPTP largely spares the dopamine neurons in the ventral tegmental area of the midbrain that project to the amygdala, olfactory tubercle, nucleus accumbens, septum, cingulate cortex, and frontal cortex [19]. However, in the mouse the olfactory tubercle was found to be altered by MPTP, although not to the degree as the striatum or substantia nigra [20, 21]. Interestingly, corticomesimal structures evidence relatively little damage in progressive supranuclear palsy, another disease with parkinsonian features that appears not to be accompanied by marked olfactory dysfunction [22].

It should be noted that the young PD control subjects of this study evidenced UPSIT scores that, although markedly abnormal, were about 5 points higher, on average, than those evidenced by the older PD patients evaluated in previous work [2, 3]. Furthermore, they evidenced detection threshold values several log units lower than those noted in earlier work.* Although these observations need to be verified using larger samples, they suggest that PD patients with a very early age of onset of symptoms may differ from PD patients with a later onset of symptoms in their ability to smell. Whether this is simply a reflection of a more resilient olfactory system in younger persons, subtle age-related progressive deterioration in olfactory function across the age range, or some other phenomenon requires additional study.

Whatever the basis for the decreased olfactory function associated with PD, the present study suggests that, on average, patients with MPTP-induced parkinsonism differ from those with the idiopathic disease in regard to their ability to smell. Whether this represents a meaningful clinical difference between PD and MPTP-induced parkinsonism is not yet known. Likewise, it is not clear whether this is support for the notion that these two conditions are, in fact, different entities. Given the current theories on the relationship between aging and PD, and the likelihood of a prolonged preclinical phase in PD [23], it will be of value in the future to determine whether patients with MPTP-induced parkinsonism eventually show decrements in the ability to smell. Furthermore, it will be useful to determine whether such decrements, should they occur, reflect decreased dopamine within corticomesolimbic or other sectors of the olfactory pathway.

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References


*It should be noted that the diluent used in the threshold series of this study was USP-grade light mineral oil, as opposed to the propylene glycol used in earlier work [2, 3]. In persons of the age range evaluated in this study, light mineral oil produces PEA threshold values approximately 0.75 log unit lower than those obtained using propylene glycol (R. L. Dory, unpublished data, 1990). Thus, the magnitude of the difference in threshold values should be adjusted by this factor before a comparison is made.


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