Pattern of dopaminergic loss in the striatum of humans with MPTP induced parkinsonism

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Abstract

Objectives—To examine the distribution of striatal dopaminergic function in humans with parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to determine if there is a caudate-putamen gradient as is seen in idiopathic Parkinson’s disease.

Methods—We scanned nine humans exposed to MPTP with parkinsonism ranging from minimal to severe using [18F]fluorodopa (FD) and high resolution PET. The results were compared with those of 10 patients with Parkinson’s disease and six normal subjects.

Results—In the MPTP group there was an equal degree of reduction of dopaminergic function in the caudate and putamen. This was different from the greater putaminal than caudate loss in Parkinson’s disease (p<0.001).

Conclusions—Parkinson’s disease is not caused by transient exposure to MPTP.

Keywords: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP); Parkinson’s disease; positron emission tomography; fluorodopa

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) produces parkinsonism in both humans and animals. Clinically, the syndrome may be almost indistinguishable with bradykinesia, rigidity, impaired postural reflexes, sometimes tremor, and a neuropsychological deficit similar to Parkinson’s disease. In some humans with parkinsonism induced by MPTP, the clinical deficit and the dopaminergic deficit as disclosed by PET, is also progressive over time.

Two control groups were scanned. The first consisted of 10 patients with Parkinson’s disease (mean age 53.6, range 33–74; four men, six women; mean MCS 22.9, range 4–44). The second consisted of six normal subjects (mean age 66.0, range 52–80; two men, four women).

This study was performed on patients who were being re-scanned on a PETT VI scanner as part of our longitudinal study reported previously. That scanner does not have sufficient resolution to examine the putamen/caudate ratio. We therefore devised a protocol where we followed the PETT VI scan with a further scan on a high resolution scanner. By 2 hours after injection 18F has decayed for more than one half life. To deal with the reduced signal we scanned on an ECAT 953–31B scanner in 3D mode. This increases the number of recorded true coincidences by a factor of six, which more than compensates for the effect of radioactive decay. The ECAT scanner has a resolution of 5.6×5.6×5 mm, full width at half

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maximum. Each image has 31 slices with a centre-centre separation of 3.375 mm. Each subject was given 100 mg carbidopa orally 1 hour before scanning. Before the PETT VI scan, the subjects were positioned in the ECAT camera using gantry mounted lasers so that the orbitomeatal line was parallel with the detector rings. An individually moulded thermoplastic face mask was then fitted to restrain head movement and to permit repositioning. Marks were made on the subject’s face mask, corresponding to the laser lines, to assist repositioning for the emission scan. A transmission scan was performed using rotating rod sources. The subject was then transferred to the PETT VI camera for a 120 minute dynamic FD scan (dose of FD 2.5–3 mCi, injected while the subject was in the PETT VI scanner). At the end of the period on the PETT VI scanner, the subjects were returned to the ECAT scanner and scanned for 15 minutes with the septae removed (3D mode). The 3D emission data were corrected for scatter using the algorithm of Bailey et al. The images were then reconstructed as a single image of 31 planes using the algorithm of Kinahan et al as implemented by Townsend et al. Regions of interest (ROIs) 8.8 mm in diameter were placed on each image—one ROI on each caudate and three ROIs distributed along each putamen. The ROIs were placed manually on the five slices where the striata were best seen. The mean bilateral caudate and putamen values were then calculated and expressed as a ratio of putamen/caudate.

**Results**

All results are from the ECAT scanner. The images from the subjects with Parkinson’s disease showed marked putaminal loss of signal with a putamen/caudate ratio of 0.68 (SD 0.053) (figs 1 and 2). By contrast, the normal subjects had a homogeneous distribution of striatal radioactivity with a putamen/caudate ratio of 1.02 (SD 0.053). The MPTP parkinsonian subjects had varying degrees of loss of striatal signal with the most severe depletion in the clinically most affected patient (fig 1). The loss was always uniform; the putamen/caudate ratio was 1.01 (SD 0.050). The severely affected patient had a ratio of 0.98. The putamen/caudate ratios in the Parkinson’s disease group were significantly different from the MPTP exposed (p=1.9 E 10, unpaired, two tailed t test on the log of the ratios) and normal groups (p=2.03 E 8). There was no difference between the putamen/caudate ratios of the MPTP exposed and normal groups. In the MPTP exposed group, there was no significant correlation between the putamen/caudate ratio and the overall severity of the dopaminergic lesion, the MCS, or with the age of the subject. The asymmetry of the ratios expressed as a percentage of the subject’s uptake varied from 0–14% (mean 5%) in the MPTP exposed group. This was significantly less than the asymmetry in the Parkinson’s disease group, which varied from 2%–23% (mean 12%, p=0.016).
The mean age and mean Columbia scores of the Parkinson’s disease group were greater than those of the MPTP exposed group. Within the Parkinson’s disease group, however, there was no correlation between the putamen/caudate ratios and either the age or the Columbia score.

Discussion

We have shown that in human MPTP induced parkinsonism there is an equal loss of dopaminergic function from the caudate and putamen. This contrasts with the greater putaminal loss seen in Parkinson’s disease both in this study and other reports.10 11 17 Other forms of parkinsonism are associated with a uniform loss of striatal signal on FD PET. In particular, in progressive supranuclear palsy there is equal loss of caudate and putaminal signal, and progressive supranuclear palsy may be distinguished from Parkinson’s disease with a high degree of certainty on the basis of the pattern of striatal FD uptake.17 25 Cortical basal ganglionic degeneration and post-traumatic parkinsonism also have a uniform loss of striatal signal in PET studies.23 26 Multiple system atrophy has a variable pattern with both uniform loss and greater putaminal loss found with PET and pathological studies.27 28

In non-human primates between the caudate and putamen, the administration of high doses of MPTP produces uniform striatal dopaminergic loss.12 By contrast, several studies have demonstrated that either a single low dose (for example, 1.5 mg/kg subcutaneously in the squirrel monkey) or chronic low doses of MPTP consistently produce a greater depletion of dopaminergic markers in the putamen than the caudate,13 29 a pattern similar to that found in Parkinson’s disease. Such a pattern was not seen in any of the subjects with MPTP induced parkinsonism in this study. Furthermore, the putamen/caudate ratio did not correlate with either the overall severity of the striatal dopaminergic lesion or the clinical deficit. Two of our subjects reported that they injected drugs that were likely to contain MPTP over 3 to 4 months, a dosing schedule similar to that administered to the monkeys, yet PET demonstrated equal caudate and putaminal loss. It is possible that one or more of the injections of MPTP administered by these subjects was a high enough dose to cause a uniform caudate and putamen dopaminergic depletion. We also found that the MPTP exposed subjects had striatal dopaminergic function that was significantly more symmetric than the subjects with Parkinson’s disease. Parkinson’s disease typically presents asymmetrically, and this is reflected in the striatal fluorodopa uptake.

It might be argued that all of our patients were exposed to the equivalent of the high doses of MPTP that produce an equal loss of caudate and putamen dopaminergic function in animal studies. However, if this were the case, we might have expected the subjects to manifest clear cut signs of parkinsonism, yet three of our subjects were initially clinically normal and gave no history of transient parkinsonism. None the less, a feature of the animal work with MPTP is the variation in degree of dopaminergic deficit that develops in response to similar doses of the toxin. It therefore remains possible that humans might develop a striatal dopaminergic deficit with a distribution similar to Parkinson’s disease if they were exposed to MPTP under different circumstances.

A further factor that needs to be considered is the effect of the subject’s age on the pattern of striatal dopaminergic loss after exposure to MPTP. The mean age of our subjects was younger than the Parkinson’s disease group, and it could be argued that the projection to the caudate is more vulnerable in younger subjects. Against this argument was the lack of any correlation between the age and the putamen/caudate ratio in the MPTP exposed group and the fact that there was an overlap in the ages of the MPTP exposed and Parkinson’s disease groups.

It is not known why there is a differential vulnerability of nigral neurons to the pathogenic process that causes Parkinson’s disease or to MPTP in some non-human primate experiments.30 There are regional differences within the nigra including variations in the concentrations of neuromelanin, calbindin, and fibroblast growth factor.31 32 There are also differences in the concentrations of dopamine reuptake sites in the striatal nerve terminals of nigral neurons. The relevance of these findings to the neuronal loss in Parkinson’s disease is not clear.33

In conclusion, the subjects of our study have a pattern of striatal dopaminergic function that differentiates them from subjects with Parkinson’s disease. This finding indicates that Parkinson’s disease is not caused by transient MPTP exposure.

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References


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