Lack of Regional Selectivity During the Progression of Parkinson Disease

Implications for Pathogenesis

Chong S. Lee, MD, FRCPC; Michael Schulzer, MD, PhD; Raul de la Fuente-Fernández, MD; Edwin Mak, MSc; Lisa Kuramoto, MSc; Vesna Sossi, PhD; Thomas J. Ruth, PhD; Donald B. Calne, MD, FRCPC; A. Jon Stoessl, MD, FRCPC

Background: Dopamine terminal loss in the putamen of patients with Parkinson disease (PD) shows a regional heterogeneity, reflecting selective vulnerability of degenerating neurons to mechanisms of cell death.

Hypothesis: If the same pathogenic mechanisms are responsible for the onset and progression of PD, the regional selectivity of dopamine cell loss will be the same throughout the course of the disorder.

Objective: To investigate the regional selectivity of dopamine terminal loss during the progression of PD.

Participants: We studied 67 patients with PD and 20 healthy subjects using positron emission tomography with \([^{11}\text{C}](\pm)dihydrotetrabenazine (DTBZ).

Results: Regional values of DTBZ binding potential (calculated as maximum specific binding \([B_{\text{max}}]\) divided by the equilibrium dissociation constant \([K_d]\)) against disease duration in the putamen of PD patients were best described by a multivariate exponential model with distinct parallel asymptotic values that were significantly \((P<.001)\) different across 4 regions of the putamen. The extent of loss of DTBZ binding potential with disease progression during the clinical stage of PD (early vs late PD) was similar between the anterior (−33%, using early PD as the baseline) and posterior (−29%) putamen. In contrast, the extent of loss of DTBZ binding potential in early PD, which reflects the cumulated loss of DTBZ binding potential from the onset of the disorder (in healthy subjects vs those with early PD), was significantly \((P<.001)\) lower in the posterior (−58%, using healthy subjects as the baseline) than the anterior (−42%) putamen.

Conclusion: To the extent that DTBZ positron emission tomography provides an accurate estimate of loss of dopamine neurons, our findings suggest that the mechanisms responsible for the progression of PD may not be the same as those responsible for its onset.

Arch Neurol. 2004;61:1920-1925

Parkinson disease (PD) is a common neurodegenerative disorder in which major pathological findings are dopamine (DA) cell loss in the substantia nigra and Lewy bodies in degenerating neurons. Nigral cell loss in PD shows a consistent pattern of regional selectivity for the caudal and ventrolateral region, leading to greater DA terminal loss in the dorsal and caudal putamen. This spatial pattern of nigrostriatal cell loss in PD is thought to derive from selective vulnerability to the mechanisms underlying cell death and, thus, could provide clues to pathogenic mechanisms.\(^3\)

Sporadic PD is generally an acquired disorder that progresses slowly during a protracted period. Mechanisms for the causation and progression of sporadic PD are largely unknown. Prevailing hypotheses include oxidative stress, mitochondrial dysfunction, inflammation, excitotoxicity, abnormal protein accumulation, and apoptosis.\(^6,9\) The problem with these hypotheses, however, is that they are not specific to PD; they cannot account for the regional selectivity of cell loss in PD. For instance, mitochondrial dysfunction, oxidative stress, accumulated protein, apoptosis, and inflammation are involved in the cell death associated with other neurodegenerative disorders, such as Alzheimer disease and amyotrophic lateral sclerosis.\(^10,14\) Mitochondrial dysfunction, oxidative stress, apoptosis, and inflammation have been proposed as pathogenic mechanisms for N-methyl-D-aspartate receptor-mediated cell death.\(^15\) yet this condition displays a different spatial pattern of nigral cell loss from PD.\(^18,19\) Moreover, oxidative stress and mitochondrial dysfunction may be involved in age-related neuronal attrition.\(^20\)
It is not clear whether the causative factors for the onset of PD also determine its progression. Thus, the same pathogenic mechanisms may cause the onset and progression of the disease. Alternatively, a transient event could cause PD and trigger secondary degenerative mechanisms responsible for prolonged progression. These kinetics of cell death have been illustrated by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine–induced parkinsonism.\(^{2,21}\)

We hypothesize that if the same mechanisms are responsible for the onset and progression of PD, the regional selectivity of DA cell loss will be the same throughout the course of the disorder. Conversely, if the progression of PD were mediated by secondary degenerative mechanisms triggered by the primary causative factor, the regional selectivity of progressive DA cell loss resulting from the secondary mechanisms may differ from that associated with the primary causative factor. In this study, we investigated the regional selectivity of DA terminal loss in the putamen of PD patients with disease progression using positron emission tomography (PET).

### METHODS

Sixty-seven patients with clinically definite PD were recruited from the Movement Disorders Clinic at the University of British Columbia according to the criteria by Calne et al.\(^{22}\) Patients were selected to represent a uniform distribution of symptom duration. Twenty age-matched healthy volunteers were included for the control group. The Table summarizes the clinical characteristics of subjects in the study. PET scans were performed using \(^{11}\)C(±)dihydrotetrabenazine (DTBZ), a ligand for the central vesicular monoamine transporter, in 3-dimensional mode (ECAT 953B/31 tomograph; CTI/Siemens, Knoxville, Tenn). On the scanning day, the subjects were off antiparkinsonian medications for at least 12 hours before PET.\(^{23}\)

The scanning procedure, data processing, and the method of image analysis are described elsewhere.\(^{24}\) The binding potential (BP) (calculated as maximum specific binding \([B_{\text{max}}]\)) divided by the equilibrium dissociation constant \(K_d\) of DTBZ was obtained from the distribution-volume ratio by subtracting 1. The study was approved by the University of British Columbia Clinical Research Ethics Committee.

To explore dynamic changes in the spatial pattern of DA terminal loss with disease progression during the clinical stage, DTBZ BP values in the 4 regions of the putamen (anterior and posterior putamen on the less and more affected sides) were regressed against symptom duration. Caudate data exhibited a large degree of variability, especially at longer durations, thus overshadowing any underlying systematic patterns of decline, possibly due in part to partial volume effects. In addition, it would be more meaningful if the kinetics of cell death were compared between cell groups in the same anatomical structure. Therefore, we included only the putamen data in this statistical analysis. We fitted jointly, for the 4 regions, a multivariate set of exponential functions of the following form:

\[
a \times \exp(-bt) + c,
\]

where \(t\) represented symptom duration in years; and \(a, b,\) and \(c\) were constants to be estimated for each region. Because of the high correlations of the PET measurements between regions within patients, univariate exponential analyses (a separate analysis of the exponential curve at each region) were inappropriate. This multivariate approach took advantage of this correlation between the measurements in different regions within patients, thus greatly increasing the precision of the analysis. Statistical analysis was performed to estimate the 3 constants in each region, to test the goodness of fit of the multivariate exponential model, and to compare the asymptotic values of the different curves between regions using special techniques of multivariate nonlinear regression.\(^{25}\) To test potential confounding “floor effects,” the data were reanalyzed with the lowest 5% and 10% of the measurements trimmed.

To compare dynamic changes in the spatial pattern of DA terminal loss during the course of PD, patients with PD were divided into 4 groups based on the duration of symptoms: PD1 (early PD), PD2, PD3, and PD4 (late PD) (Table). The anteroposterior gradient of DTBZ BP in the putamen was obtained.
by subtracting DTBZ BP of the posterior putamen (averaged over the 2 sides) from the corresponding values of the anterior putamen. The spatial pattern of DA terminal loss in the putamen that occurred during the subclinical stage from the onset of PD was estimated by comparing the anteroposterior gradient of DTBZ BP in the putamen between the healthy subjects and the early PD group (PD1) using a 2-way analysis of variance. The spatial pattern of DA terminal loss in the putamen with disease progression during the clinical stage was estimated by examining the anteroposterior gradient across the 4 duration groups of PD, using similar techniques.

The anteroposterior gradient was regressed on DTBZ and duration to rule out confounding effects of selection bias by disease severity on the dynamic changes in anteroposterior gradient with disease progression. Statistical significance was set at $P < .05$.

**RESULTS**

Figure 1 shows the scatterplots of DTBZ BP against symptom duration in 4 regions of the putamen. Figure 2 shows multivariate exponential curves that best fitted the data in each of the 4 regions analyzed (anterior and posterior putamen on the less and more affected sides). Goodness-of-fit $P$ values ranged from .89 to .99 (high $P$ values indicate good fit). The multivariate exponential model provided a significantly better fit than a multivariate linear model ($P = .03$). Reanalyses using data with the lowest 5% and 10% trimmed to compensate for potential floor effects did not change the results significantly.

The exponential decline of DTBZ BP over time occurred at roughly similar rates across 4 regions of the putamen (Figure 2). After 10 to 15 years, the DTBZ BP in all 4 curves leveled off to constant values. The constant $c$, which estimates the asymptotic values of these curves, was highly significant in each of the 4 exponential functions, and showed a significant difference between the anterior and posterior putamen and between the less and more affected sides.

Comparison of DTBZ BP in the putamen between the healthy and PD1 (early PD) groups showed a significant anteroposterior gradient across the putamen in the PD1 group ($P < .001$), leading to a significant interaction between region (anterior vs posterior putamen) and diagnosis (healthy subjects vs PD1 group) ($P < .001$) (Figure 3). In contrast, the spatial pattern of DA terminal loss that occurred during the clinical stage and was estimated by comparing the anteroposterior gradient of DTBZ BP in the putamen across 4 duration groups of PD showed no significant ($P = .17$) interaction between the region and duration groups (Figure 3). This finding is
in keeping with distinct parallel asymptotic values in the multivariate exponential model (Figure 2). Therefore, the extent of loss of DTBZ BP with disease progression during the clinical stage of PD (early vs late PD) was similar between the anterior (−33%, using early PD as the baseline) and posterior (−29%) putamen. In contrast, the extent of loss of DTBZ BP in early PD, which reflects the cumulative loss of DTBZ BP from the onset of the disorder (healthy subjects vs early PD group), was significantly (P<.001) lower in the posterior (−58%, using healthy subjects as the baseline) than anterior (−42%) putamen.

Multiple regression of the anteroposterior gradient in all PD cases on symptom duration and putaminal DTBZ BP did not show significant (P=.18) correlation between the former and the latter 2 variables.

The major finding in this study is the absence of a significant interaction between duration and anteroposterior gradient of DTBZ BP in the putamen of PD patients.

We have chosen DTBZ as a marker for DA terminal density, which is known to be less subject to regulatory changes. Although the racemic mixture of DTBZ used in this study yields less specific binding and, hence, smaller dynamic range than the active isomer, we were able to detect significant differences across duration and regions, with acceptable variance in our measures at all durations of disease.

Our findings of no significant interaction between duration and anteroposterior gradient of DTBZ BP in the putamen of PD patients could be affected by a potential floor effect in the measurements because it would reduce the anteroposterior gradient in late PD. However, the curvilinear decline of DTBZ BP stabilized at different levels in each putamen region in late PD without a tendency to converge. Furthermore, a reanalysis of the data with the lowest 5% and 10% of measured values trimmed showed similar results. These findings suggest that a floor effect is not likely to play a significant role in accounting for this lack of interaction between duration and the anteroposterior gradient.

Our cross-sectional data may be confounded by a selection bias; in particular, severe PD cases might have been underrepresented in the longer-duration group because of their greater mortality and morbidity. However, multiple regression of the anteroposterior gradient on duration and DTBZ BP in the putamen did not show a significant correlation. This lack of a significant correlation between the anteroposterior gradient and DTBZ BP indicates that the selection bias by disease severity is not likely to play a part in our findings.

Our results are consistent with observations from clinical studies that have shown a curvilinear course of progression and persistent asymmetry with disease progression. Our findings are also consistent with observations from PET and postmortem studies that show marked regional selectivity of DA cell loss in advanced PD: surviving DA terminals up to 70% of the normal [18F]dopa uptake rate constant in the ventrostral putamen and surviving nigral neurons up to nearly a quarter of the normal cell count. Therefore, we believe that our findings of no significant interaction between duration and anteroposterior gradient of DTBZ BP in the putamen of PD patients are likely to reflect a true biological phenomenon.

Our data suggest that the anteroposterior gradient of DA terminal loss in the putamen of PD patients may not change significantly with disease progression. It has been...
proposed that the spatial pattern of nigrostriatal cell loss in PD reflects the selective vulnerability of affected cells to mechanisms of cell death.\textsuperscript{3,4} Thus, the different spatial pattern of nigrostriatal cell loss between normal aging and PD has been used as evidence for the view that the aging process is not the mechanism responsible for the progression in PD.\textsuperscript{2,3,5} By analogy, our observations may be construed as evidence that the mechanisms responsible for DA terminal loss in early PD (in which there is an anteroposterior gradient within the putamen) may not be the same as those responsible for disease progression. If both mechanisms were identical, the dynamic changes in the spatial pattern of DA terminal loss during the clinical stage would have conformed to the anteroposterior gradient of DA terminal loss in early PD, which reflects the spatial pattern of cumulated DA terminal loss from the onset of the disorder. We did not find such a tendency. Our findings, therefore, are more consistent with the view that the pathogenic mechanisms responsible for the ongoing progression of PD may not be the same as the causative mechanisms responsible for the onset of PD.

This concept of biphasic mechanisms of cell death—the onset of PD due to some causative factors, followed by ongoing progression due to secondary degenerative mechanisms—is compatible with experimental evidence showing that the ongoing cell death in PD is mediated by nonspecific pathogenic mechanisms that are also proposed for other neurodegenerative disorders.\textsuperscript{10-14} This predicts that the mechanisms responsible for ongoing cell death in PD are not necessarily identical to those determining the cell type– and region-specific selective vulnerability of the disorder.\textsuperscript{36}

Although this line of thought is consistent with the current concept of mechanisms of cell death in PD, the limitations of cross-sectional data make it difficult to draw firm conclusions. Furthermore, there has been growing evidence that PD may be a heterogeneous group of disorders\textsuperscript{37} in which multiple mechanisms of cell death may work in concert.\textsuperscript{38} The kinetics of temporal and spatial progression in PD may not necessarily be uniform among proposed mechanisms of cell death and, hence, not uniform across all PD cases. Acknowledging these limitations in the present study, we cautiously conclude that our observations are consistent with the view that the natural history of PD may reflect a biphasic kinetic model: the initial causative factor is responsible for the selective pathological features of PD, and subsequent non-specific pathogenic mechanisms are responsible for ongoing cell death. Further investigations with serial observations and the addition of pathological data are required to overcome the limitations of the present study.

Accepted for Publication: June 3, 2004.

Correspondence: Chong S. Lee, MD, FRCPC, Pacific Parkinson’s Research Centre, Vancouver Hospital & Health Sciences Centre, 2221 Wesbrook Mall, Purdy Pavilion, Room M36, Vancouver, British Columbia, Canada V6T 2B5 (cslee@interchange.ubc.ca).


Funding/Support: This study was supported by grants from the Canadian Institutes for Health Research; by the Parkinson Society of British Columbia (Dr Schulzer); by the National Sciences and Engineering Research Council of Canada (Dr Sossi); by the Michael Smith Foundation for Health Research (Drs Lee and Sossi); by the Pacific Parkinson’s Research Institute (Dr Calne); and by the Canada Research Chairs program, Ottawa (Dr Stoessl). Dr Lee is a Michael Smith Foundation for Health Research Senior Scholar.

Acknowledgment: We thank TRIUMF for support; Jess McKenzie for assisting with the scanning and Susan Calne, RN, for assisting with the preparation of the manuscript.

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