Cerebral Amyloid Deposition and Serotonergic Innervation in Parkinson Disease

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Background: Prior studies suggest that serotonergic neurotransmission reduces β-amyloid (Aβ) production.

Objective: To determine whether serotonergic system degeneration in Parkinson disease promotes Aβ deposition, using in vivo positron emission tomographic probes of serotonin system integrity and Aβ deposition.

Design, Setting, and Patients: Cross-sectional study of 13 subjects with Parkinson disease from the movement disorders clinics at the University of Michigan Health System and Veterans Affairs Ann Arbor Healthcare System, with positron emission tomography using the serotonin transporter ligand carbon 11 ([11C])–labeled 3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile (DASB) and the Aβ ligand [11C]Pittsburgh compound B.

Results: Inverse correlations were found between DASB and Pittsburgh compound B distribution volume ratios in the neocortex ($r = -0.577; P = .04$) and striatum ($r = -0.780; P = .002$).

Conclusion: Serotonergic system degeneration in Parkinson disease may promote the development of cerebral amyloidopathy.


Production and deposition of β-amyloid (Aβ) are probably central to the pathogenesis of Alzheimer disease and related disorders such as dementia with Lewy bodies. Experimental evidence suggests that Aβ production is modulated by synaptic activity and by activation of specific neurotransmitter receptors, including N-methyl-D-aspartic acid receptors, M1 muscarinic cholinergic receptors, and serotonin receptors.1,2 Recent animal studies suggest that augmentation of serotonergic neurotransmission by selective serotonin reuptake inhibitors (SSRIs) may have a neuroprotective influence on the development of cerebral amyloidopathy.3 Cirrito et al6 also reported retrospective human data suggesting that SSRI use reduced Aβ deposition in humans as measured by carbon 11 ([11C])–labeled Pittsburgh compound B (PiB) positron emission tomography (PET).

These results suggest that there should be an inverse correlation between regional cerebral Aβ deposition and serotonergic innervation. Variable degeneration of serotonergic projections occurs early in Parkinson disease (PD), as does variable Aβ deposition.7,8 Regional serotonin projection integrity can be estimated in vivo with PET and the serotonin transporter ligand [11C]3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile (DASB). We performed a cross-sectional study of serotonin projection system integrity and regional Aβ deposition in 13 subjects with PD to test the hypothesis of an inverse correlation between regional serotonergic denervation and cerebral amyloidopathy.

Methods

Subjects

This study involved 13 subjects (12 male, 1 female) with PD, all of whom underwent DASB serotonin transporter and PiB Aβ PET imaging (Table 1). Subjects were recruited from the movement disorders clinics at the University of Michigan Health System and Veterans Affairs Ann Arbor Healthcare System. No subjects in our cohort were on serotonergic medications at enrollment or at the time of PET imaging. No subjects endorsed a previous history of antidepressant use. All subjects met the
UK Parkinson Disease Society Brain Bank clinical diagnostic criteria for PD. Diagnosis of PD was confirmed by the presence of typical nigrostriatal dopaminergic denervation on [11C]dihydrotetrabenazine (DTBZ) PET imaging. Subjects underwent a detailed clinical evaluation, including physical examination by a movement disorders specialist. The University of Michigan Institutional Review Board approved this study.

IMAGING TECHNIQUES

All subjects underwent brain magnetic resonance imaging for anatomic coregistration, DTBZ-PET, DASB-PET, and PiB-PET.

Magnetic resonance imaging was performed on a 3-T Achieva system (Philips) using an 8-channel head coil and the ISQOX examination card protocol primarily designed to yield isotropic spatial resolution. A standard T1-weighted series of a 3-dimensional inversion recovery–prepared turbo field echo was performed in the sagittal plane using the following parameters: repetition time, 9.8 milliseconds; echo time, 4.6 milliseconds; inversion time, 1041 milliseconds; turbo factor, 200; single average; field of view, 240 × 200 × 160 mm; and acquired matrix, 240 × 200. One hundred sixty slices were reconstructed to 1-mm isotropic resolution. This sequence maximizes contrast among gray matter, white matter, and cerebrospinal fluid and provides high-resolution delineation of cortical and subcortical structures.

Imaging with DTBZ-PET, DASB-PET, and PiB-PET was performed in 3-dimensional imaging mode using an ECAT HR+ tomograph (Siemens Molecular Imaging, Inc), which acquires 63 transaxial slices (slice thickness, 2.4 mm; intrinsic in-plane resolution, 4.1 mm; full width at half maximum; 15.2-cm axial field of view). A NeuroShield head holder and shielding unit (Scanwell Systems) was attached to the patient’s bed to reduce the contribution of detected photon events originating from the body outside the scanner’s field of view. Prior to DTBZ, DASB, and PiB injections, a 3-minute transmission scan was acquired using rotating germanium 68 rods for attenuation correction of emission data using the standard vendor-supplied segmentation and reprojection routines. All subjects were studied in the supine position, with eyes and ears unoccluded, resting quietly in a dimly lit room.

Monoaminergic DTBZ was prepared as reported previously. Dynamic PET scanning was performed for 60 minutes immediately following a bolus injection of 55% of a 555-MBq (18 mCi) dose of (+)-[11C]DTBZ (containing <50 μg of cold DTBZ mass) over the first 15 to 30 seconds of the study, while the remaining 45% of the dose was continuously infused over the next 60 minutes, resulting in stable arterial tracer levels and equilibrium with brain tracer levels after 30 minutes. A series of 15 scan frames over 60 minutes was obtained as the following: 4 scan frames over 30 seconds; 3 scan frames over 1 minute; 2 scan frames over 2.5 minutes; 2 scan frames over 5 minutes; 2 scan frames over 10 minutes; 4 scan frames over 10 minutes.

Serotoninergic DASB-PET studies were acquired as 17 sequential emission scans. A series of 17 scan frames over 80 minutes was obtained as the following: 4 scan frames over 30 seconds; 3 scan frames over 1 minute; 2 scan frames over 2.5 minutes; 2 scan frames over 5 minutes; and 6 scan frames over 10 minutes. Radiotracer was administered as a bolus (666 MBq [18 mCi] of [11C]DASB containing <8 μg of cold DASB) plus constant infusion using 70% as a slow bolus over 30 seconds, followed by constant infusion of the remaining 30% over the 80-minute study duration. The Aβ [11C]PiB-PET scans were performed similarly using a bolus and infusion protocol acquiring 17 frames over 80 minutes, with a priming bolus of 40% of the radioactive dose followed by continuous infusion of the remaining 60% over the 80-minute study using a dose of 666 MBq (18 mCi). Ten of 13 subjects had DASB-PET and PiB-PET scans acquired on the same day, with the longest interval between scans being 70 days.

Interactive Data Language image analysis software (Research Systems Inc) was used to manually trace volumes of interest (VOIs) on magnetic resonance images including the striatum and cerebellum. Mesencephalic VOIs were defined by the mean of the substantia nigra and midbrain raphe complex. Total neocortical VOI was defined using semiautomated threshold delineation of the cortical gray matter signal. All image frames were spatially coregistered within subjects with a rigid-body transformation to reduce the effects of subject motion during the imaging session. Motion-corrected PET frames were spatially coregistered to the T1-weighted magnetic resonance image using standard coregistration procedures in SPM8b implemented in Matlab 2010b software (MathWorks). Time activity curves for each VOI were generated from the spatially aligned PET frames. The DTBZ, DASB, and PiB distribution volume ratios (DVRs) were estimated by the Logan plot graphical analysis method, with the time-activity curves as the input function and with the inferior posterior cerebellum as reference tissue for both PiB and DASB and the neocortex as reference tissue for [11C]DBTZ. Spearman rank order correlation was used to estimate the association between DASB and PiB DVR values (SAS version 9.1 statistical software; SAS Institute, Inc). Multiple regression analysis with rank transformation of striatal DASB and DTBZ was used to determine whether findings of striatal amyloidopathy are associated with these 2 markers of progressive neurodegeneration in PD.

An inverse relationship between the DASB and PiB DVRs was noted in the cortex (ρ = −0.577; P = .04) and striatum (ρ = −0.780; P = .002). The Figure shows the distribution of the neocortical and striatal DASB and PiB DVRs for the 13 subjects in our cohort. Table 2 shows Spearman correlation coefficients between the PiB and DASB DVRs in the 2 regions of interest. Table 3 shows limited region-specific DVRs for DTBZ-PET, DASB-PET, and PiB-PET.

To explore whether the association between regional serotoninergic terminal integrity and amyloidopathy was attributable to advancing nonspecific neurodegeneration, we performed multiple regression analysis using a rank transformation for each variable to allow for linear regression of striatal findings, with PiB DVR as the depen-
The inverse correlations between neocortical and striatal amyloid burden and neocortical and striatal serotoninergic terminal integrity should be reflected in similar correlations between mesencephalic DASB and supratentorial amyloid binding. Therefore, a post hoc analysis was performed. It confirmed the relationship between mesencephalic serotoninergic system integrity (the primary source of forebrain serotoninergic projections) and cortical and striatal amyloid burden (cortex: $\rho = -0.615$, $P = .02$; striatum: $\rho = -0.681$, $P = .01$) (Table 2).

Our results suggest that the degree of regional forebrain serotoninergic denervation correlates inversely with neocortical and striatal cerebral amyloidopathy in PD. These findings are consistent with those of Cirrito et al, who described decreased amyloid burden in cognitively normal elderly subjects with a history of SSRI treatment compared with cognitively normal elderly subjects without a history of SSRI treatment. This group also demonstrated that SSRI treatment reduces brain interstitial fluid Aβ levels and amyloid plaque deposition in a murine transgenic Alzheimer disease model. Prior experimental in vitro and murine genetic model studies indicated that increasing serotoninergic neurotransmission reduces Aβ production and deposition.  

Strong association between regional serotoninergic denervation and amyloidopathy was found in both the striatum and the neocortex. The relatively large size of these VOIs, particularly the neocortical VOI, provides robust statistics for our analyses. Post hoc analysis of midbrain DASB binding is also consistent with an inverse association between amyloid burden and serotonin system pathology. Prominent striatal changes may reflect the pathology of amyloidopathy in PD without dementia, which is characterized by greater involvement of the striatum compared with the neocortex. Longitudinal DASB-PET and PiB-PET studies of cognitively normal elderly subjects with varying amyloid burden may be useful in assessing relationships between serotoninergic projection integrity and amyloidopathy.

Limitations of our study include our small sample size and cross-sectional design, which can suggest only an association rather than a causal relationship between serotoninergic system degeneration and amyloidopathy. The gender distribution within our cohort (12 male, 1 female) was skewed, which may relate to an increased prevalence of PD among men as well as subject recruitment from a Veterans Affairs Healthcare System clinic. We also note that we are interpreting a decreased DASB DVR as evidence of terminal degeneration, although it could conceivably represent dysregulation of the serotonin transporter expression within intact presynaptic terminals. Given strong postmortem evidence for loss of serotoninergic perikarya in PD, we feel this possibility is less likely. Another limitation was that subjects eligible for this study were at risk for cognitive impairment based

**Table 2. Spearman Correlation Coefficients Between Regional DASB and PiB Distribution Volume Ratios**

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>$\rho$</th>
<th>$P$ Value</th>
</tr>
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<tbody>
<tr>
<td>Cortical PiB and cortical DASB</td>
<td>-0.577</td>
<td>.04</td>
</tr>
<tr>
<td>Cortical PiB and midbrain DASB</td>
<td>-0.615</td>
<td>.02</td>
</tr>
<tr>
<td>Striatal PiB and striatal DASB</td>
<td>-0.780</td>
<td>.002</td>
</tr>
<tr>
<td>Striatal PiB and midbrain DASB</td>
<td>-0.681</td>
<td>.01</td>
</tr>
</tbody>
</table>

**Table 3. Distribution Volume Ratios of DTBZ, DASB, and PiB for Each Region of Interest**

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>DVR, Mean (SD)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>DTBZ</td>
</tr>
<tr>
<td>Striatum</td>
<td>1.972 (0.326)</td>
</tr>
<tr>
<td>Neocortex</td>
<td>1.118 (0.106)</td>
</tr>
<tr>
<td>Midbrain</td>
<td>2.467 (0.388)</td>
</tr>
</tbody>
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Abbreviations: DASB, carbon $^{11}$-labeled 3-amino-4-(2-dimethylaminoethyl-phenylsulfanyl)-benzonitrile; DTBZ, carbon $^{11}$-labeled dihydrotetrabenazine; DVR, distribution volume ratio; PiB, carbon $^{11}$-labeled Pittsburgh compound B.
on older age, balance impairments, or cognitive symptoms. This sample may not be representative of the PD population at large.

Our results support the concept that serotoninergic neurotransmission is a physiologically relevant modulator of Aβ production. If this idea is correct, it may help to explain variations in Aβ deposition found in PD, PD with dementia, and dementia with Lewy bodies. Larger studies are needed to confirm this association. Longitudinal observational studies are needed to determine the relationship between serotonin terminal integrity and progressive cerebral amyloidopathy. Our results also support the idea that manipulation of serotoninergic neurotransmission with well-tolerated agents such as SSRIs is a viable investigational approach to preventing or slowing Aβ production and deposition.

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Author Contributions: Dr Kotagal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kotagal, Frey, and Albin. Acquisition of data: Kotagal, Bohnen, Müller, and Koeppe. Analysis and interpretation of data: Kotagal, Bohnen, Müller, Koeppe, Frey, and Albin. Drafting of the manuscript: Kotagal and Albin. Critical revision of the manuscript for important intellectual content: Kotagal, Bohnen, Müller, Koeppe, Frey, and Albin. Statistical analysis: Kotagal, Bohnen, Müller, and Koeppe. Obtained funding: Bohnen, Frey, and Albin. Administrative, technical, and material support: Koeppe. Study supervision: Bohnen, Müller, and Albin.

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REFERENCES