Alterations of Striatal Dopamine Receptor Binding in Alzheimer Disease Are Associated With Lewy Body Pathology and Antemortem Psychosis

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Background: Lewy bodies (LB) are present in at least 20% to 30% of persons with Alzheimer disease (AD) and contribute to the risk of psychosis and to excess cognitive burden.

Objective: To determine whether altered striatal dopamine receptor binding is associated with LB and psychosis in AD.

Design: Postmortem case control.

Setting: Alzheimer’s Disease Research Center at the University of Pittsburgh (Pa).

Participants: Consecutive cases from the Alzheimer’s Disease Research Center brain bank, neuroleptic free for at least 1 month prior to death, with neuropathologic diagnoses of AD with LB (AD+LB, n=14), AD without LB (AD, n=13), or normal brains (n=8).

Main Outcome Measures: Dopamine D1, D2, and D3 receptor densities, and affinities as determined by selective saturation binding studies in striatal tissue.

Results: Subjects with AD+LB, compared with those with AD, demonstrated increased D1 receptor density and decreased D2 and D3 receptor density. D3 receptor density was selectively increased, however, in AD subjects with a history of psychosis, independent of the presence or absence of LB. The effect of neuroleptic treatment on D3 binding was further examined in an additional group of subjects who had received neuroleptics near the time of death. Neuroleptic treatment reduced D3 affinity with no effect on D3 density.

Conclusions: Alzheimer disease with LB is associated with selective alterations in dopamine receptor density, which may contribute to the distinct clinical profile of this group. The D3 receptor may be an important target of neuroleptic treatment of psychosis in AD.

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Alzheimer disease (AD) is currently estimated to affect 3 to 4 million individuals in the United States. Psychotic symptoms, delusions, and hallucinations occur in at least 30% to 40% of AD patients. Patients with AD and psychotic symptoms demonstrate more severe cognitive deficits than matched AD subjects without psychosis. Similarly, AD subjects with psychotic symptoms are at risk for more rapid cognitive deterioration and more rapid decline in function, and premature institutionalization.

Many individuals diagnosed antemortem with AD will demonstrate cortical Lewy bodies (LB) at autopsy in addition to the neuropathologic findings of AD (AD with Lewy bodies, AD+LB). Alzheimer disease with Lewy bodies has been associated with excess cognitive burden, extrapyramidal symptoms, and with more frequent psychotic symptoms. Prominent reductions in postmortem measures of presynaptic dopamine have been reported in AD+LB. These reductions, however, are not as severe as seen in Parkinson disease.

A limited number of studies have examined dopamine receptor density in AD subjects who have been characterized with regard to LB. Dopamine D1, D2, and D3 receptors, but not D4 or D5 receptors, are expressed in striatum. Perry et al examined nonselective D2/D3 receptor binding using [3H]raclopride in AD, AD+LB, and normal control (NC) subjects. Neuroleptic-naïve or neuroleptic-intolerant AD+LB subjects had reduced striatal D2/D3 receptor binding, while AD subjects did not differ from NC subjects. Whether the observed reductions in D2/D3 binding were due to a reduction in D2 binding, in D3 binding, or in both cannot be directly answered at this time. Because D3 density var-
SUBJECTS AND METHODS

MATERIALS

The radioligands iodine \(^{[125I]}\) (R)-trans-7-hydroxy-2-[(N-4-propyl-N-(3'-iodo-2'-propenyl)amino)tetralin \((^{[125I]}\)trans-7-OH-PIPAT) and \([^{3}H]\) SCH23390 were obtained from NEN Life Science Products, Boston, Mass. Ketanserin, \((+)-\)butaclamol hydrochloride and PD-128907 were obtained from Research Biochemicals International, Natick, Mass. Ultima Gold scintillation fluid was obtained from Packard Instrument Co, Meriden, Conn. Anti-B(A4) peptide was provided by the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) and purchased from Dr Henryk Wisniewski, New York State Institute for Basic Research, Staten Island. Antibodies to a-synuclein were provided by Dr Virginia M.-Y. Lee, University of Pennsylvania, Philadelphia.

CLINICAL CHARACTERIZATION OF SUBJECTS

Subjects were identified through the brain bank of the Alzheimer’s Disease Research Center at the University of Pittsburgh. All studies were approved by the institutional review board of the University of Pittsburgh. Of the 27 AD and AD+LB subjects, 25 underwent complete neurologic, neuropsychologic, and psychiatric diagnostic evaluations at initial and annual evaluations as part of their participation in the Alzheimer’s Disease Research Center. Details of these assessment protocols have been reported elsewhere.\(^{5,6,11}\) In addition, all available records were reviewed for evidence of delusions and hallucinations by 1 of 2 raters (R.A.S., M.T.H.). Interrater reliability for the classification of psychosis was established in 20 subjects and was high (\(k = 0.70\)). Delusions and hallucinations were defined as previously described.\(^{10,17}\) No patient had a history of schizophrenia, schizoaffective disorder, or other idiopathic psychosis. Extrapyramidal symptoms were defined by the presence of bradykinesia, cogwheel rigidity, or resting tremor. Extrapyramidal symptom ratings were unavailable for 3 AD+LB subjects. Current medications were recorded at all Alzheimer’s Disease Research Center visits. In addition, psychotropic medications used in the past (initial visit) or since the last evaluation (annual visits) were recorded. Medications used at the time of death and during the 3 months prior to death were reviewed, and the interval since last neuroleptic use was recorded.

Demographic and clinical information for the 8 NC, 13 AD, and 14 AD+LB subjects are presented in Table 1. All subjects were either neuroleptic naive (\(n = 30\)) or neuroleptic free for at least 1 month (\(n = 5\)). Lifetime duration of neuroleptic treatment did not differ between groups (exact multinomial, \(P = 0.80\)). Normal control subjects were significantly younger (mean [SD], 66 [14] years, \(F_{2} = 5.5, P < 0.01\)), with nearly significantly longer mean [SD] postmortem intervals (6 [3] days, \(F_{2} = 3.1, P = 0.06\)), and more often men (100%, exact multinomial, \(P = 0.001\)) compared with AD subjects. There were no significant differences in these variables between the AD and AD+LB groups or in Braak score,\(^{16}\) a measure of neurofibrillary pathology (\(F_{1} = 0.3, P = 0.90\)).

BRAIN TISSUE PROCESSING AND NEUROPATHOLOGIC DIAGNOSES

At the time of brain removal, postmortem interval was recorded and the brain was divided in the midsagittal plane. The right hemibrain was coronally sectioned at 1.0-cm intervals. The majority of the right nucleus accumbens in each case was dissected and divided into 3 frozen samples, 1 of which was used for this study. The head of the right caudate was sampled from the same section. All samples were stored at −80°C until assayed. The left hemibrain was fixed in 10% formalin, then sectioned coronally. The tissue sections examined, and the histologic and immunocytochemical methods used, followed CERAD protocols and have been described in detail elsewhere.\(^{17}\) Neuritic plaques, diffuse plaques, and neurofibrillary tangles were semiquantitatively scored and diagnoses established using CERAD criteria.\(^{16}\) A diagnosis of AD+LB further required multiple a-synuclein–positive LB in limbic and/or neocortical areas. Conversely, a diagnosis of AD indicated that no a-synuclein–positive LB were present in any area, including the substantia nigra.

ies along a dorsal to ventral gradient in striatum,\(^{12}\) the absence of a significant interaction of striatal region with the diagnostic group in the examination of D2/D3 binding reported by Perry et al\(^{10}\) provides indirect evidence that both D2 and D3 binding were reduced.

Joyce et al\(^{13}\) examined D1 and D2 receptor binding in striatum of AD and NC subjects. Alzheimer disease was not associated with reduction in striatal D2 receptor binding, unless the AD subjects also demonstrated extrapyramidal symptoms (EPS). D2 binding in AD did not differ from controls, and there was no association with EPS. In contrast, D1 binding was elevated in response to the dopamine deficit found in Parkinson disease.\(^{13,14}\) The hypothesis that D3 binding is also elevated in response to the less extensive dopamine deficit seen in AD+LB has not been examined.

Although older studies reporting elevated D2/D3/D4 receptor binding to be associated with schizophrenic psychosis were confounded by long-term neuroleptic exposure, recent evidence suggests the D2 receptor may play a role in psychotic symptoms. There is a significant association of schizophrenia with homozygosity for a biallelic Ball/MscI polymorphism in the D2 gene, although the magnitude of this association is modest.\(^{15}\) Similarly, we found homozygosity for this polymorphism to be associated with a modest increased rate of psychosis in subjects with AD.\(^{16}\) Increased striatal D2 binding has been reported in subjects with schizophrenia who are not taking neuroleptics in comparison with NC subjects, with the largest differences in rostral-ventral striatum.\(^{17}\) Neuroleptic treatment was associated with normalization of D3 binding.\(^{17}\) In contrast to schizophrenia, the association of D3 receptor binding with psychosis in AD has not been examined.

We undertook, therefore, saturation binding studies of D1, D2, and D3 receptors in neuroleptic-free NC,
AD, and AD+LB subjects characterized with regard to their history of psychotic symptoms. We hypothesized that AD+LB would be associated with reduced density of both D1 and D2 receptors, with a corresponding increased D1 density. We further hypothesized that increased D1 density would be associated with a history of psychotic symptoms in both AD and AD+LB subjects.

**RESULTS**

The association of receptor densities and affinities with neuropathologic group is presented in Figure 1. There was a significant difference among groups in D3 density ($F_2=3.5$, $P=.04$) and D1 affinity ($F_2=3.3$, $P=.04$). Mean (SEM) covariate-adjusted D1 densities were 34% higher in AD+LB vs AD subjects, 21.7 (1.5) vs 16.2 (1.6), respectively ($P=.01$). When D1 affinity was included as a covariate, the association of D1 density with diagnostic group was reduced but continued to demonstrate a significant trend ($F_2=3.2$, $P=.06$). D1 density also demonstrated a trend toward a significant difference among groups ($F_2=3.2$, $P=.06$). Mean covariate-adjusted D2 densities were 30% lower in AD+LB than AD subjects, 11.9 (2.0) and 18.8 (2.0), respectively ($P=.02$). D2 affinity differed significantly among groups ($F_2=4.1$, $P=.03$), with significantly higher affinity in AD and AD+LB vs NC subjects ($P=.03$ and $P=.009$, respectively). After entering D2 affinity as a covariate, the association of D2 density with diagnostic group was significant ($F_2=4.2$, $P=.03$). D2 density did not differ among groups ($F_2=2.2$, $P=.10$). However, D2 affinity was significantly different among groups ($F_2=4.3$, $P=.03$). Post hoc comparisons revealed a significant difference between the AD+LB and NC groups ($P=.02$). After inclusion of D2 affinity as a covariate, there remained no significant association of D2 density with diagnostic group ($F_2=2.0$, $P=.20$).

There were no significant associations of density or affinity of any of the receptors with EPS in AD subjects. Similarly, neither D1 density and affinity nor D2 density and affinity were associated with psychosis in the AD sub-

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**STATISTICAL ANALYSIS**

$B_{max}$ and $K_d$ were determined by nonlinear regression analysis of specific binding using GraphPad Prism software. All binding studies were best fit by a 1-site model, which was confirmed by both statistical comparison of fits and by visual inspection of Scatchard transformations. Statistical analyses used Statistical Product and Service Solutions for Windows 9.0.0 (SPSS Inc, Chicago, Ill). $K_d$ was transformed to $pK_d$ ($-\log K_d$) for all analyses. $B_{max}$ and $pK_d$ for each receptor were the dependent variables. The association of $B_{max}$ and $pK_d$ with diagnostic group was tested by analysis of covariance, with age, postmortem interval, and sex entered as covariates. A covariate indicating the tissue homogenization method (see above) was entered in all analyses. Tests of the associations of $B_{max}$ and $pK_d$ with psychosis and EPS used 2-way analysis of covariance with diagnosis and psychosis (or EPS) presence-absence entered as cofactors. Age, postmortem interval, and sex were not included in tests restricted to AD and AD+LB subjects, as these groups were matched on these variables.

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**SATURATION BINDING ASSAYS**

For all assays, unwashed tissue was used to preserve the original tissue density of dopamine receptors. Caudate and nucleus accumbens samples were ground into powder over liquid nitrogen. At onset of the study, samples were weighed, thawed, then homogenized and suspended in buffer the morning of each assay day. Later the homogenization step was performed immediately prior to addition to the assay tubes. This methodologic change was treated as a covariate in all statistical analyses. Total and nonspecific binding at each concentration of ligand were determined in triplicate.

$D_1$ assays were conducted as described by Hall et al with minor modifications. Total volume was 500 µL, with a final concentration of caudate tissue of 2.0 mg wet weight per milliliter. Incubation buffer was 50-mmol/L tris-hydrochloride (pH 7.4), 120-mmol/L sodium chloride, 1-mmol/L magnesium chloride, 2-mmol/L calcium chloride, 5-mmol/L potassium chloride, and 0.1% ascorbic acid. Ketanserin, 200 nmol/L, was added to block binding to serotonin2A receptors. The ligand was $[\text{3H}]-\text{SCH23390}$, 0.25 to 8.0 nmol/L. Nonspecific binding was defined by 1-µmol/L domperidone. Both $D_1$ and $D_2$ assays included in tests restricted to AD and AD+LB subjects, as these groups (F2=4.2, P=.03) and 18.8 (2.0), respectively (P=.02). $D_2$ affinity differed significantly among groups (F2=4.1, P=.03), with significantly higher affinity in AD and AD+LB vs NC subjects (P=.03 and P=.009, respectively). After entering D2 affinity as a covariate, the association of D2 density with diagnostic group was significant (F2=4.2, P=.03). D2 density did not differ among groups (F2=2.2, P=.10). However, D2 affinity was significantly different among groups (F2=4.3, P=.03). Post hoc comparisons revealed a significant difference between the AD+LB and NC groups (P=.02). After inclusion of D2 affinity as a covariate, there remained no significant association of D2 density with diagnostic group (F2=2.0, P=.20).

There were no significant associations of density or affinity of any of the receptors with EPS in AD subjects. Similarly, neither D1 density and affinity nor D2 density and affinity were associated with psychosis in the AD sub-

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In contrast, D3 density was significantly elevated among subjects with psychosis (F1 = 5.8, P = .03, Figure 2). Controlling for the presence of psychosis, there was also a significant reduction of D3 density in the AD+LB compared with AD subjects (F1 = 6.9, P = .02). In contrast, D3 affinity was not associated with psychosis (F1 = 1.2, P = .30), although a significant increase in D3 affinity was present in AD+LB compared with AD subjects (F1 = 11.0, P = .006). There was also a significant interaction of psychosis and diagnosis (F1 = 10.5, P = .007). The associations of D3 density with psychosis and diagnostic group were unaltered when D3 affinity was entered as a covariate (F1 = 5.7, P = .03 and F1 = 5.0, P = .04, respectively). Mean [SD] covariate-adjusted D3 densities were increased by 72% in subjects with psychosis (6.9 [1.0]) compared with those without psychosis (4.0 [0.7]). In contrast, mean covariate-adjusted D3 densities were decreased by 52% in AD+LB subjects vs AD subjects, 3.5 (1.0) and 7.3 (1.1), respectively.

We identified 6 subjects who had been excluded from the above analyses due to recent neuroleptic use. The clinical characteristics of these patients are presented in Table 2. All neuroleptic-treated subjects were diagnosed as having AD+LB. They did not differ significantly in age, sex, race, Braak score, or history of psychosis from the 9 AD+LB subjects not taking neuroleptics in whom D3 assays were conducted (Table 1). D3 density and affinity for the AD+LB subjects treated with and without neuroleptics are presented in Figure 3.
was no effect of neuroleptic treatment on $D_3$ density ($F_1=2.0, P=0.2$). However, $D_3$ affinity was significantly reduced in the neuroleptic-treated subjects ($F_1=5.8, P=0.03$). In 1 subject treated with neuroleptics, neuroleptic use was 16 days prior to death. Exclusion of this subject had almost no effect on mean $[SD]$ $D_3$ affinity in the neuroleptic-treated group ($pK_d=8.63$ [0.3]), and the difference between groups in $D_3$ affinity continued to show a trend toward significance ($P=0.08$).

Consistent with our hypotheses, the presence of LB in AD subjects was associated with increased density of caudate $D_1$ receptors, reduced density of nucleus accumbens $D_3$ receptors, and a trend toward reduced density of caudate $D_2$ receptors. Alzheimer disease with LB was also associated with an increased affinity of all 3 dopamine receptors, although the changes in receptor density were unaffected by the observed changes in affinity. In contrast to the association of altered receptor binding with AD+LB, $D_3$ receptor density was elevated in subjects with a history of psychosis, independent of the presence or absence of Lewy bodies.

The observed alterations in $D_1$ and $D_3$ density may result, in part, from a postsynaptic response to sustained striatal dopamine deficits, which have been observed in AD+LB. 8-10,25,26 Although we did not measure striatal dopamine concentration directly, the observed increase in receptor affinities in AD+LB is consistent with reduced dopamine concentration in caudate and nucleus accumbens of these subjects. 27 In the prototype dopamine deficiency disorder, Parkinson disease, caudate $D_1$ density is typically up-regulated in untreated subjects by 40% to 50%. 14 The effect of dopamine deficiency on the $D_1$ receptor is not well established, although recent evidence indicates that $D_1$ binding is down-regulated by about 40% to 50% in caudate and nucleus accumbens of patients with Parkinson disease. 28

In contrast to $D_1$ and $D_3$, the trend toward reduction in $D_2$ density is not consistent with a postsynaptic response to dopamine depletion. In Parkinson disease, caudate $D_2$ density is typically up-regulated in untreated subjects by 15% to 80%. 14,27 The extent of dopamine deficiency in AD+LB is not as severe as is seen in Parkinson disease. 3 Thus, it is possible that $D_2$ receptors are not up-regulated in response to moderate concentration decreases, possibly due to lower affinity for dopamine than $D_1$ and $D_3$. 28 Absent up-regulation, however, does not explain the observed reduction in $D_2$ density. We have described numerous $\alpha$-synuclein-positive neurites in striatum of AD+LB. 30 Whether this

**Figure 1.** Dopamine receptor density and affinity in subjects with Alzheimer disease with cortical Lewy body pathology (AD+LB) and those with AD only. A, $D_3$ density is elevated in AD+LB. The difference between groups in $D_2$ density approached significance ($P=0.06$). The groups did not differ in $D_1$ density. Asterisk indicates $P<0.05$ for the effect of diagnostic group; dagger, $P<0.05$ vs AD on post hoc test. B, The groups differed significantly in affinity for all 3 receptors, with AD+LB subjects having the highest $D_2$ and $D_3$ affinities. Asterisk indicates $P<0.05$ for the effect of diagnostic group; dagger, $P<0.05$ vs normal controls (NC) on post hoc test.

**Figure 2.** $D_3$ density and affinity in subjects with Alzheimer disease (AD) stratified according to the presence of cortical Lewy bodies (LB) and history of psychosis. A, $D_3$ density is elevated in subjects with psychosis with or without LB. After accounting for the effect of psychosis, $D_3$ density is reduced in subjects with AD with cortical LB pathology (AD+LB) vs those only with AD. Asterisk indicates AD+LB vs AD, $P<0.05$; dagger, subjects with psychosis vs those without psychosis, $P<0.05$. B, After accounting for the effect of psychosis, $D_3$ affinity is higher in subjects with AD+LB. The interaction of diagnostic group $\times$ psychosis is also significant.
pathologic process preferentially affects D_2 pathways is not known.

We also found that having accounted for the effect of LB presence on D_3 receptor binding, there was a significant increase in D_3 density in subjects with a history of psychosis. The increase in D_3 density in psychosis was present in both AD and AD+LB subjects and unaffected by D_1 affinity. Overall, subjects with psychosis had a 72% elevation in mean D_3 density compared with subjects without psychosis. The magnitude of this elevation is consistent with the report of a 55% to 110% increase in D_3 receptor density in ventral striatum. Thus, the most parsimonious explanation of the effect of neuroleptic treatment on D_3 density is that it acts to “down-regulation” of D_3 binding. Because autoradiographic binding is dependent on both receptor density and affinity, the reduced D_3 binding interpreted by Gurevich et al could have resulted from an affinity reduction. The mean D_3 K_1 in our subjects taking neuroleptics was 2.4 times higher than in subjects not taking neuroleptics (3.1 nmol/L and 1.3 nmol/L, respectively). This difference would yield an approximate 100% difference in D_3 density. *Asterisk indicates P<.05 for subjects taking neuroleptics vs those not taking neuroleptics.

Whether elevated D_3 density in psychosis is a primary deficit or reflects a pathologic response to other disease-related processes cannot be determined. However, the elevations in D_3 density do not appear to be an artifact of neuroleptic treatment. In contrast to findings for the D_2 receptor in striatum, striatal D_3 receptor binding is not up-regulated by antipsychotic treatment in animals. Similarly, we found no effect of recent neuroleptic treatment on D_3 density in our psychotic subjects, indicating the specificity of our observation.

In contrast to the absence of neuroleptic effects on D_3 density, we found that D_3 affinity was reduced by neuroleptic treatment. This latter finding may explain an apparent discrepancy between the present study and that by Gurevich et al. Using receptor autoradiography, they found that neuroleptic treatment at the time of death led to a significant decrease in D_3 affinity. Asterisk indicates P<.05 for subjects taking neuroleptics vs those not taking neuroleptics.

### Table 2. D_3 Receptor Binding Characteristics in Alzheimer Disease Subjects With Cortical Lewy Bodies Who Were Receiving Neuroleptic Treatment at the Time of Death*

<table>
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<th>Age, y</th>
<th>Sex</th>
<th>PMI, h</th>
<th>Braak Score</th>
<th>Days Since Last Neuroleptic Use</th>
<th>Neuroleptic and Dosage, mg/d</th>
<th>Lifetime Duration of Neuroleptic Use, mo</th>
<th>Ever Psychotic</th>
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*PMI indicates postmortem interval. All subjects were white. Column totals represent mean ± SD.
an alternate mechanism (e.g., posttranslational modification) remains unknown.

An important limitation of the present study is that most AD and AD+LB subjects had advanced dementia at the time of autopsy. We cannot conclude that the observed dopamine receptor changes are present in earlier stages of illness when the clinical profiles of AD and AD+LB diverge. Another limitation of our study is the inexact matching of the NC subjects, which may have reduced the magnitude of detectable difference between groups because of the need to enter covariates into the analyses. We did not find an association of decreased D2 density with EPS in our subjects. This may have resulted from limited power due to the small number of subjects with EPS, rather than a lack of true association. 0.13 Strengths of the present study include the ante mortem behavioral characterization of the subjects, examination of multiple receptor populations in the same subjects, and the use of saturation binding methods that provide separate information about affinity and density.

In conclusion, this study provides evidence for a distinct pattern of expression of striatal D1, D2, and D3 receptors in AD+LB. Future studies would benefit from inclusion of a Parkinson disease comparison group. Further studies examining the D3 receptor as a target of neuroleptic action are indicated.

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