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

Robert A. Sweet, MD; Ronald L. Hamilton, MD; Matthew T. Healy, MEd; Stephen R. Wisniewski, PhD; Ruth Henteleff, AB; Bruce G. Pollock, MD, PhD; David A. Lewis, MD; Steven T. DeKosky, MD

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.

Arch Neurol. 2001;58:466-472

From the Division of Geriatrics and Neuropsychiatry (Drs Sweet, Pollock, and DeKosky, Mr Healy, and Ms Henteleff), Department of Psychiatry (Dr Lewis), and the Division of Neuropathology, Department of Pathology (Dr Hamilton), School of Medicine, and the Department of Epidemiology, Graduate School of Public Health (Dr Wisniewski), University of Pittsburgh, Pittsburgh, Pa.

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 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-naive 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 $^{[125]}$(R)-trans-7-hydroxy-2-[N-(3'-iodo-2'-propeny1)amino]tetralin ($^{[125]}$trans-7-OH-PIPAT) and $^{[3H]}$-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 α-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.5,16,17 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 (κ = 0.70). Delusions and hallucinations were defined as previously described.16,17 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 = .80). Normal control subjects were significantly younger (mean [SD], 66 [14] years, F2=5.5, P<.01), with nearly significantly longer mean [SD] postmortem intervals (6 [3] days, F2=3.1, P=.06), and more often men (100%, exact multinomial P<.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 (F1=.03, P=.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 Neurotic plaques, diffuse plaques, and neurofibrillary tangles were semiquantitatively scored and diagnoses established using CERAD criteria.18 A diagnosis of AD+LB further required multiple α-synuclein–positive LB in limbic and/or neocortical areas. Conversely, a diagnosis of AD indicated that no α-synuclein–positive LB were present in any area, including the substantia nigra.

Continued on next page
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 D3 density. We further hypothesized that increased D3 density would be associated with a history of psychotic symptoms in both AD and AD+LB subjects.

The association of receptor densities and affinities with neuropathologic group is presented in Figure 1. There was a significant difference among groups in D1 density ($F_2=3.3$, $P=.04$) and D2 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 ($F_2=3.2$, $P=.06$). D2 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 ($F_2=4.2$, $P=.03$). D3 density did not differ among groups ($F_2=2.2$, $P=.10$). However, D3 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 D3 affinity as a covariate, there remained no significant association of D3 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-

**RESULTS**

**SATURATION BINDING ASSAYS**

For all assays, unwashed tissue was used to preserve the original tissue density of dopamine receptors.20 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$_2$ assays were conducted as described by Hall et al$^{21}$ 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 mM L-tris-hydrochloride (pH 7.4), 120 mM sodium chloride, 1 mM magnesium chloride, 2 mM L-calcium chloride, 5 mM potassium chloride, and 0.1% ascorbic acid. Ketanserin, 200 nmol/L, was added to block binding to serotonin$_2A$ receptors. The ligand was [3H]-SCH23390, and 0.25 to 8.0 nmol/L. Nonspecific binding was defined by 1-µmol/L domperidone. Both D1 and D2 assays were conducted in a total volume of 500 µL, with a final concentration of caudate tissue of 2 mg wet weight per milliliter. Incubation buffer was 50 mM L-tris-hydrochloride (pH 7.4), 120 mM sodium chloride, 2 mM L-calcium chloride, 1.5 mM L-magnesium chloride, and 300 µM guanosine triphosphate. The ligand was [3H]-raclopride, 0.07 to 40.0 nmol/L. To block D1 binding, 50 µL of 5.0-µmol/L PD128907 (final concentration, 0.5 µmol/L) was added to each tube. Nonspecific binding was defined by 1-µmol/L (+)-butaclamol. D$_3$ assays were conducted in a total volume of 500 µL, with a final concentration of caudate tissue of 2 mg wet weight per milliliter. Incubation buffer was 50 mM L-tris-hydrochloride (pH 7.4), 120 mM sodium chloride, 2 mM L-calcium chloride, 1.5 mM L-magnesium chloride, and 300 µM guanosine triphosphate. The ligand was [3H]-raclopride, 0.07 to 40.0 nmol/L. To block D1 binding, 50 µL of 5.0-µmol/L PD128907 (final concentration, 0.5 µmol/L) was added to each tube. Nonspecific binding was defined by 1-µmol/L domperidone. Both D$_3$ and D$_2$ assays were incubated at room temperature for 60 minutes and terminated by placing tubes in an ice water bath. Samples were harvested onto filter strips (Whatman GF/B; Whatman Inc, Newton, Mass), which had been soaked in 0.5% poly (ethyleneimine) solution, then washed with 12-mL ice cold 50 mM L-tris-hydrochloride solution (pH 7.4). Filters were placed into scintillation vials with 4.0-mL scintillation fluid and counted for 5 minutes in a scintillation counter (Beckman LS-5801; Beckman, Fullerton, Calif).

D$_3$ assays were conducted adapting the methods Gurevich et al$^{21}$ and Pugsley et al$^{22}$ for selective labeling of D$_3$ receptors, and used tissue from nucleus accumbens. Total volume was 100 µL, with a final tissue concentration of 10 mg wet weight per milliliter. Incubation buffer was 50 mM L-tris-hydrochloride (pH 7.4), 0.50 mM L-EDTA, 120 mM L-sodium chloride, 1.0 mM L-magnesium chloride, 1.5 mM L-calcium chloride, and 300 µM guanosine triphosphate. The ligand was [3H]-trans-7-OH-PHIPAT, 0.125 to 8.0 nmol/L. Nonspecific binding was defined by 0.50 µmol/L PD128907. Under these conditions, binding to receptors other than D$_3$ (eg, D$_1$, serotonin$_1A$, or sigma sites) is eliminated.$^{21,22}$ Assays were incubated at room temperature for 90 minutes, then terminated and harvested as described above. Filters were counted for 1 minute in a gamma counter (Tietertek).

**STATISTICAL ANALYSIS**

$B_{max}$ and $K_d$ were determined by nonlinear regression analysis of specific binding using GraphPad Prism software.$^{24}$ 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.
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 < .001). 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 5 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 D1 density (F1=2.0, P=0.2). However, D3 affinity was significantly reduced in the neuroleptic-treated subjects (F1=5.8, P=.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] D3 affinity in the neuroleptic-treated group (pKd=8.63 [0.3]), and the difference between groups in D3 affinity continued to show a trend toward significance (P=.08).

**COMMENT**

Consistent with our hypotheses, the presence of LB in AD subjects was associated with increased density of caudate D1 receptors, reduced density of nucleus accumbens D3 receptors, and a trend toward reduced density of caudate D2 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, D1 receptor density was elevated in subjects with a history of psychosis, independent of the presence or absence of Lewy bodies.

The observed alterations in D1 and D3 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 D1 density is typically up-regulated in untreated subjects by 40% to 50%.14 The effect of dopamine deficiency on the D3 receptor is not well established, although recent evidence indicates that D3 binding is down-regulated by about 40% to 50% in caudate and nucleus accumbens of patients with Parkinson disease.28

In contrast to D1 and D3, the trend toward reduction in D2 density is not consistent with a postsynaptic response to dopamine depletion. In Parkinson disease, caudate D2 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 D2 receptors are not up-regulated in response to moderate concentration decreases, possibly due to lower affinity for dopamine than D1 and D3.26 Absent up-regulation, however, does not explain the observed reduction in D2 density. We have described numerous α-synuclein–positive neurites in striatum of AD+LB.30 Whether this
pathologic process preferentially affects D2 pathways is not known.

We also found that having accounted for the effect of LB presence on D3 receptor binding, there was a significant increase in D3 density in subjects with a history of psychosis. The increase in D3 density in psychosis was present in both AD and AD+LB subjects and unaffected by D2 affinity. Overall, subjects with psychosis had a 72% elevation of mean D3 density compared with subjects without psychosis. The magnitude of this elevation is consistent with the report of a 55% to 110% increase in D3 receptor binding, measured by autoradiography, in ventral striatum of subjects with schizophrenic psychosis who were not taking neuroleptics. Guided by our studies of the association of psychosis with genetic variation in the D3 receptor, we had hypothesized that D3 plays a permissive role in the onset of psychotic symptoms in subjects with an underlying neurodevelopmental or neurodegenerative condition. The findings of the present study, taken together with those of Gurevich et al, provide support for this hypothesis in 3 disorders: schizophrenia, AD, and AD+LB. The magnitude of the association of psychosis with striatal D3 density is substantially greater than that of the association of psychosis with homozygosity for the Ball polymorphism in the D3 gene. This suggests that the contribution of the Ball polymorphism to the determination of D3 density in brain is modest. Consistent with this interpretation, we did not find a significant association between D3 density and genotype in these subjects (data not shown).

Whether elevated D3 density in psychosis is a primary deficit or reflects a pathologic response to other disease-related processes cannot be determined. However, the elevations in D3 density do not appear to be an artifact of neuroleptic treatment. In contrast to findings for the D2 receptor in striatum, striatal D2 receptor binding is not up-regulated by antipsychotic treatment in animals. Similarly, we found no effect of recent neuroleptic treatment on D3 density in our subjects. Finally, there was no corresponding up-regulation of D2 receptors in our psychotic subjects, indicating the specificity of our observation.

In contrast to the absence of neuroleptic effects on D3 density, we found that D3 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 “down-regulation” of D3 binding. Because autoradiographic binding is dependent on both receptor density and affinity, the reduced D3 binding interpreted by Gurevich et al could have resulted from an affinity reduction. The mean D3 Kd 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 D3 affinity. Asterisk indicates P= .05 for subjects taking neuroleptics vs those not taking neuroleptics.

**Table 2. D3 Receptor Binding Characteristics in Alzheimer Disease Subjects With Cortical Lewy Bodies Who Were Receiving Neuroleptic Treatment at the Time of Death**

<table>
<thead>
<tr>
<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>
<th>D3 Bmax, fmol/mg Tissue</th>
<th>D3 pKd, pM</th>
</tr>
</thead>
<tbody>
<tr>
<td>83</td>
<td>F</td>
<td>1.33</td>
<td>4</td>
<td>16</td>
<td>Risperidone, 1.5</td>
<td>8</td>
<td>Yes</td>
<td>6.25</td>
<td>8.46</td>
</tr>
<tr>
<td>69</td>
<td>M</td>
<td>4.00</td>
<td>6</td>
<td>3</td>
<td>Thioridazine, 50</td>
<td>&gt;36</td>
<td>No</td>
<td>9.88</td>
<td>8.14</td>
</tr>
<tr>
<td>81</td>
<td>M</td>
<td>5.75</td>
<td>5</td>
<td>4</td>
<td>Haloperidol, 0.5</td>
<td>67</td>
<td>Yes</td>
<td>4.44</td>
<td>8.91</td>
</tr>
<tr>
<td>71</td>
<td>M</td>
<td>9.00</td>
<td>3</td>
<td>0</td>
<td>Risperidone, 3.0</td>
<td>&gt;12</td>
<td>Yes</td>
<td>1.41</td>
<td>8.79</td>
</tr>
<tr>
<td>79</td>
<td>M</td>
<td>7.00</td>
<td>5</td>
<td>4</td>
<td>Risperidone, 0.5</td>
<td>6</td>
<td>No</td>
<td>6.15</td>
<td>8.68</td>
</tr>
</tbody>
</table>

*A PMI indicates postmortem interval. All subjects were white. Column totals represent mean ± SD.*

Figure 3. The effect of neuroleptic use at the time of death on D3 density (A) and affinity (B). There was no significant effect of neuroleptic treatment at time of death on D3 density. In contrast, neuroleptic treatment resulted in a significant decrease in D3 affinity. Asterisk indicates P=.05 for subjects taking neuroleptics vs those not taking neuroleptics.
an alternate mechanism (eg, 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.10,13 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 neurexoptics action are indicated.

Accepted for publication June 12, 2000.

This work was supported in part by grants MH01153 and AG15133 from the National Institutes of Health and grant M1998-003 from the John F. and Nancy A. Emmerling fund of The Pittsburgh Foundation.

Corresponding author and reprints: Robert A. Sweet, MD, Western Psychiatric Institute and Clinic, 3811 O'Hara St, Pittsburgh, PA 15213 (e-mail: Sweetra@msx.upmc.edu).

REFERENCES

28. Ryojo HL, Pierrotti D, Joyce JN. Dopamine D3 receptor is decreased and D2 receptor is elevated in the striatum of Parkinson’s disease. Mov Disord. 1998;13:788-797.