PET Imaging of Serotonin Type 2A Receptors in Late-Life Neuropsychiatric Disorders

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Objective: To determine whether there are abnormalities in the in vivo status of the serotonin type 2A (5-HT_{2A}) receptor in late-life depression and Alzheimer's disease, the authors used positron emission tomography (PET) to assess patients with these two conditions and healthy subjects. Method: PET was performed by using \textsuperscript{[18}F]altanserin to evaluate 5-HT_{2A} receptor binding in 11 elderly patients with depression (four men, seven women; mean age=65.0 years, SD=5.5); nine Alzheimer's disease patients, including three with concurrent depression (two men, seven women; mean age=69.7 years, SD=5.0); and 10 age-matched healthy subjects (four men, six women; mean age=69.8 years, SD=5.0). Partial-volume correction of regional specific binding estimates was performed by using a method based on magnetic resonance imaging. Results: No significant abnormalities in \textsuperscript{[18}F]altanserin binding (binding potential) were observed in the patients with late-life depression, and no effect of depression on binding potential was present within the Alzheimer's disease group. However, the patients with Alzheimer's disease had significantly lower binding than the normal subjects in several brain regions, including the anterior cingulate, prefrontal cortex, and sensorimotor cortex. Conclusions: These results suggest that the 5-HT_{2A} receptor is differentially affected in late-life depression and Alzheimer's disease, a finding that has implications for the etiological basis of mood and cognitive features of neuropsychiatric disorders of late life.


Geriatric depression is a complex disorder in which many potential contributing factors are implicated. These include age- or disease-related changes in brain function and structure, medical comorbidity, and cognitive dysfunction. There also exists an empirical link between depression in later life and Alzheimer's disease. Depression occurring in the elderly is frequently accompanied by cognitive impairment and is associated with an increased risk of developing Alzheimer's disease (1). Conversely, Alzheimer's disease patients have a high prevalence of coexisting depression (2). Whether they have a common underlying biological mechanism is yet undetermined; however, there is substantial evidence to associate abnormalities in serotonergic function with both disorders.

Dysregulation of the serotonin (5-HT) neurotransmitter system has been specifically implicated in depressive illness. In particular, considerable evidence indicates that the type 2A (5-HT_{2A}) receptor subtype has an important although poorly defined role in depressive illness and the mechanism of antidepressant medication (3–6). Selective degeneration of the 5-HT system, particularly the 5-HT_{2A} receptor, has also been linked to both mood and cognitive features of Alzheimer's disease (7–10). In postmortem specimens, Bowen et al. (11) found diminished 5-HT_{2A} receptor density in the brains of both elderly depressed and Alzheimer's disease patients.
In vivo human data related to the role of the 5-HT$_{2A}$ receptor in late-life neuropsychiatric disorders are limited. Substantially lower than normal specific binding has been shown in moderately to severely demented subjects with Alzheimer’s disease by using positron emission tomography (PET) and [${}^{18}$F]altanserin (12). Biver et al. (13) recently used PET imaging to demonstrate significantly lower than normal binding of [${}^{18}$F]altanserin to right orbitofrontal 5-HT$_{2A}$ receptors in a group of midlife depressed subjects, although to our knowledge comparable studies of the elderly have not been performed.

Substantial aging effects on the 5-HT system, and particularly the 5-HT$_{2A}$ receptor, have been observed in both animals and human postmortem studies (14–18). We and others (19, 20) have demonstrated a marked age-related decline in specific binding of [${}^{18}$F]altanserin to 5-HT$_{2A}$ receptors in humans in vivo. This finding supports the hypothesis that age-related changes in 5-HT function predispose the elderly to develop depression and suggests a continuum of serotonergic losses in normal aging, late-life depression, and Alzheimer’s disease. The purpose of this work was to test this hypothesis and thus to determine whether there are differences in 5-HT$_{2A}$ binding among nondemented depressed elders, Alzheimer’s disease patients, and age-matched healthy subjects.

**METHOD**

**Subjects**

Eleven untreated elderly depressed patients were referred for a PET study from the Mental Health Clinical Research Center for Late-Life Mood Disorders at the University of Pittsburgh before starting antidepressant therapy. Nine mildly to moderately demented patients with probable Alzheimer’s disease according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (21) were recruited from the Alzheimer’s Disease Research Center at the University of Pittsburgh. Three of the Alzheimer’s disease patients also had concurrent depression. All depressed subjects met the DSM-IV criteria for current major depressive episode (nonpsychotic). The diagnosis of depression was established by an interview with a research psychiatrist and expert consensus evaluation. Information on clinical and demographic variables is shown in table 1. A comparison group of 10 healthy elderly subjects was recruited through the use of advertisements and from ongoing studies of aging at our institution. The subjects in the comparison group were screened for evidence of dementia or past or present depression. Normal subjects who had first-degree relatives with psychiatric or neurodegenerative disorders were also excluded from study participation. All subjects were free of significant medical burden, neurological disease, and history of head trauma, substance abuse, or seizure disorder. With the exception of three Alzheimer’s disease patients who were taking donepezil (5 mg daily), individuals using psychotropic or other medications with known central effects, including beta-blockers, were not studied. The subjects were instructed to refrain from the use of nonprescription cold preparations for a minimum of 1 week before the PET study. None of the female subjects was receiving estrogen replacement therapy.

The evaluation included the Mini-Mental State (22), Hamilton Depression Rating Scale (23), and Mattis Organic Mental Syndrome Screening Examination (24). The score on the Hamilton depression scale was not available for one subject in the comparison group. The Mattis examination was not given to two nondemented depressed subjects who were free of clinical evidence of dementia. The depressed subjects were entered into an ongoing therapeutic trial and were tested weekly with the Hamilton depression scale during the course of supervised treatment with either nortriptyline or paroxetine. After complete description of the study to the subjects, written informed consent was obtained before study entry, in compliance with the procedures of the University of Pittsburgh Institutional Review Board.

**PET Imaging and Data Acquisition**

Radiosynthesis of [${}^{18}$F]altanserin was performed according to the method of Lemaire et al. (25). Dynamic PET scanning was performed for 90 minutes after a bolus intravenous injection of 10-mCi high-specific-activity (≥1.04 Ci/μmol) [${}^{18}$F]altanserin. Emission data were collected by using a Siemens 951R/31 tomograph (CTI PET Systems, Knoxville, Tenn.), which acquires images in 31 parallel planes with an interplane separation of 3.4 mm, in two-dimensional imaging mode (septa extended). Head movement was minimized by the use of a thermoplastic mask and head-holder system. Dynamic arterial blood sampling was performed by means of a 21-gauge radial artery catheter. The arterial input function, for the kinetic analyses, consisted of approximately 35 0.5-mL hand-drawn samples collected over the scanning interval (including 20 samples in the initial 2 minutes after injection). The blood samples were centrifuged, and the plasma radioactivity concentration was measured. Additionally, 3-mL blood samples were acquired at 2 minutes 20 seconds and then...
at 10, 30, 60, and 90 minutes after \[^{18}F\]altanserin injection, for the determination of the fraction of unmetabolized \[^{18}F\]altanserin (of the total plasma radioactivity concentration) over time by means of high-performance liquid chromatography. A 10-minute transmission scan was acquired by using rotating rods of \[^{68}Ge/^{68}Ga\] immediately before \[^{18}F\]altanserin injection and was used for attenuation correction of the emission data. The PET data were also corrected for radioactive decay and scatter and were reconstructed with a Hanning window and a cutoff at 0.8 of the Nyquist rate.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI), performed on a Signa 1.5-T scanner (GE Medical Systems, Milwaukee) with a standard head coil, was used for guiding the selection of regions of interest and for partial-volume correction of the PET data. After a scout T\(_2\)-weighted sagittal sequence, a volumetric spoiled gradient recalled sequence (TE=5 msec, TR=25 msec, flip angle=40°, number of excitations=1, field of view=24 cm, image matrix=256 \times 192 pixels) was acquired in the coronal plane. The spoiled gradient recalled magnetic resonance (MR) images were used for all analyses; however, fast spin echo T\(_2\)- and proton-density-weighted images were also acquired and were reviewed by a neuroradiologist (C.C.M.) for evidence of prior cerebral infarction or other significant neuropathology. Pixels that corresponded to the scalp and calvarium were removed from the spoiled gradient recalled MR images (26) before registration with the PET images. PET-MRI registration was performed according to the method of Woods et al. (27), as further validated in our laboratory (28).

Data Analysis

Selection of regions of interest. Regions of interest were hand drawn on the coregistered MR images and transferred to the dynamic PET data to generate time-activity curves. Twelve regions were selected: anterior cingulate, pregenual cingulate, subgenual cingulate, sensorimotor cortex, parietal cortex, amygdalohippocampal complex, lateral temporal cortex, medial orbitofrontal cortex, lateral orbitofrontal cortex, prefrontal cortex, occipital cortex, and striatum (figure 1). Data for paired right and left regions of interest were recorded individually and also as averaged values. Several of these regions were selected because of a priori hypotheses of possible involvement of 5-HT\(_{2A}\) receptors in specific brain areas in depression (e.g., anterior cingulate, subgenual cingulate, amygdalohippocampal complex, lateral temporal cortex, medial orbitofrontal cortex, lateral orbitofrontal cortex, prefrontal cortex, occipital cortex, and striatum) (3, 4, 20, 29), while others (e.g., striatum, occipital cortex) were chosen for comparison with areas with lower known specific binding and/or a low suspicion of abnormalities related to Alzheimer’s disease or depression (30). The regions of interest in the cerebellar hemispheres at the level of the fourth ventricle were also sampled; owing to the relatively low 5-HT\(_{2A}\) receptor concentrations in the cerebellum (30), this brain area was selected as a reference region and used to approximate the free concentration and nonspecific binding of \[^{18}F\]altanserin (19, 31, 32). The plasma data were corrected for the presence of radiolabeled metabolites of \[^{18}F\]altanserin as determined by high-performance liquid chromatography analyses (32–34).

Tracer kinetic modeling. As described previously and applied in studies of both young and elderly healthy persons (19, 31), the PET data were modeled according to the Logan graphical analysis method (35, 36). Estimates of specific binding measures obtained
TABLE 2. Regional Tissue-Correction Factors for Atrophy Correction of 5-HT2A Specific Binding in Brains of Patients With Late-Life Depression or Alzheimer’s Disease and Age-Matched Healthy Comparison Subjects

<table>
<thead>
<tr>
<th>Region</th>
<th>Depressed (N=11)</th>
<th>Alzheimer’s Disease (N=9)*</th>
<th>Comparison (N=10)</th>
<th>Tissue-Correction Factor (lower value indicates greater atrophy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cingulate</td>
<td>0.86 0.06</td>
<td>0.77 0.08</td>
<td>0.86 0.04</td>
<td>0.77 0.04</td>
</tr>
<tr>
<td>Pregenual cingulate</td>
<td>0.89 0.07</td>
<td>0.80 0.08</td>
<td>0.87 0.07</td>
<td>0.80 0.07</td>
</tr>
<tr>
<td>Subgenual cingulate</td>
<td>0.92 0.04</td>
<td>0.84 0.07</td>
<td>0.90 0.07</td>
<td>0.87 0.07</td>
</tr>
<tr>
<td>Lateral orbitofrontal</td>
<td>0.77 0.04</td>
<td>0.73 0.05</td>
<td>0.78 0.05</td>
<td>0.76 0.06</td>
</tr>
<tr>
<td>Lateral temporal</td>
<td>0.79 0.06</td>
<td>0.70 0.07</td>
<td>0.76 0.06</td>
<td>0.76 0.06</td>
</tr>
<tr>
<td>Amygdalohippocampal</td>
<td>0.87 0.05</td>
<td>0.80 0.06</td>
<td>0.88 0.04</td>
<td>0.80 0.06</td>
</tr>
<tr>
<td>Occipital</td>
<td>0.86 0.05</td>
<td>0.80 0.09</td>
<td>0.83 0.07</td>
<td>0.80 0.07</td>
</tr>
<tr>
<td>Medial orbitofrontal</td>
<td>0.82 0.04</td>
<td>0.79 0.05</td>
<td>0.82 0.05</td>
<td>0.81 0.05</td>
</tr>
<tr>
<td>Parietal</td>
<td>0.82 0.05</td>
<td>0.78 0.07</td>
<td>0.81 0.07</td>
<td>0.77 0.06</td>
</tr>
<tr>
<td>Prefrontal</td>
<td>0.68 0.05</td>
<td>0.65 0.05</td>
<td>0.70 0.05</td>
<td>0.69 0.05</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>0.80 0.05</td>
<td>0.74 0.06</td>
<td>0.77 0.06</td>
<td>0.70 0.06</td>
</tr>
<tr>
<td>Striatum</td>
<td>0.92 0.01</td>
<td>0.90 0.02</td>
<td>0.93 0.01</td>
<td>0.90 0.01</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.89 0.03</td>
<td>0.88 0.06</td>
<td>0.89 0.04</td>
<td>0.86 0.07</td>
</tr>
</tbody>
</table>

*a* Includes three depressed patients.

*b* Significantly lower than value for one or both other groups (p<0.05, Tukey’s post hoc test, error df=27).

with this method are generally less variable than those obtained by using nonlinear least-squares curve-fitting methods (31, 37, 38). Time-activity data for each region of interest (ROI) over the 10 to 90 minutes following injection were used to obtain estimates of the radioligand distribution volume (DV) and apparent binding potential (BP), where BP = (DVROI/DVcerebellum) – 1. The regional distribution volume was expressed in relation to the cerebellar distribution volume to minimize the influence of plasma and tissue nonspecific binding (35). The binding potential, which is proportional to the concentration of available receptors (B’ max) and the equilibrium dissociation constant (Kb), was the outcome measure of interest.

Partial-volume correction. Because of the prominent cerebral atrophy in Alzheimer’s disease (39, 40) and potential differences in cerebrovascular volume between patients with late-life depression and normal elderly subjects (41–43), an MRI-based partial-volume correction (44) was applied to the Logan binding potential values according to a previously described method (19). Regional tissue-correction factors were generated by sampling regions of interest in individualized MRI-generated brain tissue images representative of the distribution of brain and nonbrain voxels, at a spatial resolution similar to that of the PET data (in-plane full width at half maximum = 10.3 mm, z-axis full width at half maximum = 5.9 mm). Partial-volume correction of the regional binding potential values was performed by dividing the binding potential by its corresponding tissue-correction factor.

Statistical analysis. Because of the small subject groups encountered when we subdivided the Alzheimer’s disease group by the presence of depression, a nonparametric Mann-Whitney U test was applied to the [18F]altanserin PET data from both the nondepressed and depressed Alzheimer’s disease patients, to establish similarities. Demeating graphic characteristics were examined and compared across diagnostic groups by means of either a chi-square test for categorical data (gender) or analysis of variance (ANOVA) for continuous data (age, education). With controls for age and gender, an independent univariate ANOVA was used to examine group differences in atrophy-corrected binding potential among the three main subject groups. This was followed by post hoc univariate (ANOVA) comparisons with age and gender assigned as covariates. To explore potential regional differences between the right and left hemispheres, we performed a repeated measures ANOVA with right and left binding potential as the repeated measure. To verify the need to correct for atrophy, particularly in the Alzheimer’s disease subjects, ANOVAs were also applied to assess group differences in the regional tissue-correction factors.

We also performed correlations between atrophy-corrected binding potential and possible sources of patient variability. Spearman correlations were applied to determine whether a relationship existed between regional binding potential and severity of depression as determined by scores on the Hamilton depression scale for the nondepressed depressed subjects. Spearman correlations were also conducted to determine whether baseline binding potential predicted speed of recovery in the depressed group, defined by time (weeks) until achievement of a Hamilton depression scale score of 10. In addition, we performed correlations between Mini-Mental State scores and atrophy-corrected binding potential for the Alzheimer’s disease group.

Also, repeated measures ANOVA was applied to determine whether there was a significant difference between subject groups in the rate of peripheral metabolism of [18F]altanserin. For this analysis, the three groups’ percentages of unchanged altanserin in plasma (as determined by high-performance liquid chromatography) were compared at each of the sampled time points (2.3, 10, 30, 60, and 90 minutes). Potential differences in nonspecific binding of [18F]altanserin among the subject groups was assessed by ANOVA. For all analyses, statistical significance was set at p<0.05 owing to the relatively small number of brain regions investigated.

RESULTS

There were no significant gender (χ²=0.75, df=2, n.s.) or age (F=2.91, df=2, 27, p=0.07) differences among the three subject groups, although the nondemented depressed patients tended to be younger than the normal or Alzheimer’s disease subjects (table 1). The comparison group was generally better educated than the patients (F=5.90, df=2, 27, p=0.007).

Using ANOVA followed by Tukey’s post hoc tests, we observed significant differences in the magnitude of the regional tissue-correction factors among the three groups. The Alzheimer’s disease subjects had significantly lower values (i.e., greater atrophy) than the comparison group and/or the nondemented depressed group in several brain regions (table 2). These included the anterior cingulate (F=5.54, df=2, 27, p=0.01), pregenual cingulate (F=5.78, df=2, 27, p=0.01), subgenual cingulate (F=5.06, df=2, 27, p=0.02), striatum (F=7.89, df=2, 27, p=0.002), lateral orbitofrontal cortex (F=5.46, df=2, 27, p=0.01), lateral temporal cortex (F=6.42, df=2, 27, p=0.005), amygdalohippocampal complex (F=7.46, df=2, 27, p=0.003), prefrontal cortex (F=3.96, df=2, 27, p=0.03), and sensorimotor cortex (F=4.14, df=2, 27, p=0.03). The tissue-correction factors did not significantly differ between the nondemented depressed subjects and the comparison group in any region.

Overall, regional specific binding followed the known rank order of 5-HT2A receptor density (30). After an initial ANOVA of the data revealed no group-by-hemisphere interactions (p>0.15), paired right and left regions of interest were averaged for subsequent analyses. There were no significant differences in corrected binding potential between the nondemented depressed patients and the normal comparison group in any brain region examined (figure 2 and figure 3). No effect of depression on binding potential was noted in the nondemented depressed subjects or within the Alzheimer’s disease group; therefore, the Alzheimer’s disease subjects with and without depression were
pooled for further analyses. The patients with Alzheimer’s disease had significantly lower atrophy-corrected binding potential than both the nondemented depressed and comparison groups in several brain areas, according to ANOVA. These regions were the anterior cingulate (F=3.74, df=2, 25, p=0.04), prefrontal cortex (F=4.65, df=2, 25, p=0.02), and sensorimotor cortex (F=3.75, df=2, 25, p=0.04). In addition, the atrophy-corrected binding potential in the Alzheimer’s disease group was significantly lower than that of the nondemented depressed patients but not the comparison group in the lateral temporal cortex (F=3.35, df=2, 25, p=0.05) and amygdalohippocampal complex (F=4.15, df=2, 22, p=0.03).

The cerebellar distribution volumes, representative of the free radioligand concentration and nonspecific binding, did not differ significantly among the nondemented patients with late-life depression (mean=1.69, SD=0.54), patients with Alzheimer’s disease (mean=1.94, SD=0.53), and comparison subjects (mean=1.68, SD=0.50) (F=0.71, df=2, 27, p=0.50).

No effect of subject group was observed in the rate of metabolism of [18F]altanserin in plasma (F=0.04, df=2, 26, p=0.76). At 2 minutes 20 seconds postinjection, similar mean fractions of the parent compound were measured in the plasma of the normal subjects (mean=96.0%, SD=2.2%), nondemented depressed patients (mean=96.1%, SD=2.0%), and patients with Alzheimer’s disease (mean=94.9%, SD=3.7%). At the end of the 90-minute scanning period, the average fraction of unchanged [18F]altanserin was 42.7% (SD=6.2%) in the comparison group, 42.0% (SD=16.2%) in the depressed patients, and 45.3% (SD=10.8%) in the Alzheimer’s disease group. Although radiolabeled metabolites of [18F]altanserin appear to cross the blood-brain barrier, these metabolites have been demonstrated to have no significant specific binding to the 5-HT2A receptor in vivo and, therefore, contribute to free radioligand concentration and nonspecific binding only (31–34).

The correlations between regional binding potential for [18F]altanserin and Hamilton depression scale score or time to recovery in the depressed patients did not achieve statistical significance. Also, no statistically significant correlations between binding potential and Mini-Mental State scores for the Alzheimer’s disease subjects were observed.

DISCUSSION

The major finding of this work is the absence of a significant abnormality in central 5-HT2A receptor binding of [18F]altanserin in late-life depression, in contrast to significantly lower than normal binding in Alzheimer’s disease. This suggests that the 5-HT2A receptor may not play a key role in depressive illness and differs from the finding of a specific regional [18F]altanserin binding abnormality in midlife depression by Biver et al. (13). In work by Biver et al. (13), statistical parametric mapping techniques were applied to PET images from eight midlife depressed patients and 22 healthy comparison subjects. These data showed significantly lower uptake of [18F]altanserin in a brain region encompassing the right orbitofrontal cortex and anterior portion of the insula in the depressed patients; a similar trend was observed in the homologous region in the left hemisphere. An analogous brain region (lateral orbitofrontal cortex) was sampled in the current study by using a region-of-interest approach; no specific binding differences were found between the elderly nondemented depressed patients and the age-matched comparison group. The study of Biver et al. (13) supports the theory that 5-HT2A receptor activity is impaired in depressive illness; however, the potential influence of age-related factors on the PET measurements was not fully considered and thus may potentially confound their interpretation. First, the mean age of the patients was 10 years higher than that of the nondepressed comparison group. Given the steep age-related decline in 5-HT2A binding that has been demonstrated with [18F]altanserin PET imaging (19, 20), it is possible that the age difference between the subject groups may, in part, have accounted for the apparent differences in depression-related binding. Second, although structural brain differences would be expected to be small in the midlife group studied, the finding of significant binding differences in a brain region adjacent to a major (Sylvian) fissure raises the issue of the potential dilutional influence of greater age-related cerebral volume loss in the depressed subjects than the younger comparison group. In the current study, the subjects in the comparison group were slightly older than the depressed patients.

![FIGURE 2. Selected Coregistered MRI and Parametric [18F]Altanserin PET Brain Images of 5-HT2A Binding Potential in a 61-Year-Old Healthy Comparison Man, 64-Year-Old Depressed Man, and 67-Year-Old Man With Probable Alzheimer’s Disease](image-url)
overall, but the subjects’ ages were restricted to a total interval of 18 years (58–76 years of age), and the potential influence of age on the binding estimates was accounted for in the statistical analysis. Further, the effect of possible age-related differences in cerebral volume loss on the PET measurements was accounted for by correcting the data for partial-volume effects.

In addition to a small (but nonsignificant) age difference between subject groups, reports of accentuated brain atrophy in late-life depression (41–43) reinforced the need to correct the PET measurements for the potential dilutional effect of cerebral atrophy. However, the lack of a significant difference in regional tissue-correction factors between the nondemented depressed and comparison groups suggested that the abnormalities in cerebral volume in depression were small, and indeed, they did not alter the study results. Substantial atrophy did exist in several regions in the Alzheimer’s disease group. Therefore, atrophy correction was applied to all data to eliminate this source of bias in the PET measurements. A previous PET study (12) indicating 5-HT_{2A} receptor abnormalities in Alzheimer’s disease examined moderately to severely demented patients but did not correct for the potential confounding effects of greater atrophy in the patients than in the normal elderly subjects.

In postmortem studies by Bowen and colleagues (11), late-life depression was associated with low 5-HT_{2A} receptor binding in several cortical regions (temporal, frontal, parietal). Greater differences from normal were seen in the brains of patients with Alzheimer’s disease, although these may be in part due to the fact that the Alzheimer’s disease patients were older (mean age=82 years) than both the comparison group and the nondemented depressed patients. Also, the results of such postmortem studies are likely to be biased toward Alzheimer’s disease of end-stage severity. In the current study, the low number of subjects precluded a definitive examination of 5-HT_{2A} receptor status in patients with coincident depression and Alzheimer’s disease. However, the absence of an abnormality in [^{18}F]altanserin binding in the nondemented depressed group, coupled with the lack of evidence for an effect of depression within the Alzheimer’s disease group, suggests that the 5-HT_{2A} receptor is differentially affected in late-life depression and Alzheimer’s disease. Potential reasons for conflicting findings in late-life depression between the work of Bowen et al. (11) and the present in vivo study include the inherent difficulty in postmortem studies of ensuring uniform selection of subjects with uncomplicated major depression and controlling for exposure to psychotropic medications. Although the possibility of a type 1 error due to limited sample size in the PET study must be considered, the group sizes were sufficiently large to detect an approximately 30% difference in regional binding measures in the lateral orbitofrontal cortex between the late-life depressed and comparison groups. This magnitude was consistent with our expected effect size based on postmortem studies of similar brain regions in suicide victims (3, 45). Further, there was no evidence for trends in any of the regional binding measures suggesting a difference between the late-life depressed subjects and the comparison group (figure 3).

There is substantial evidence to support the influence of gender on the functional status of the 5-HT system (46–49). Particularly relevant to this study is the reported contribution of postmenopausal decreases in estrogen levels to alterations in circulating 5-HT and

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**FIGURE 3.** Atrophy-Corrected 5-HT_{2A} Binding Potential in Brain Regions of Patients With Late-Life Depression or Alzheimer’s Disease and Age-Matched Healthy Comparison Subjects

- **Comparison (N=10)**
- **Depressed (N=11)**
- **Alzheimer’s disease (N=9)**

*Significantly lower than value for one or both other groups (p<0.05, Tukey’s post hoc test; includes three depressed subjects in Alzheimer’s disease group).*
central 5-HT$_{2A}$ receptor densities in women (46, 49, 50). For these reasons, the influence of gender on [18F]altanserin binding to 5-HT$_{2A}$ receptors was considered. An effort was made to minimize the potential confounding impact of gender on the PET measurements by gender matching the subject groups (depressed patients: 36% male, Alzheimer’s disease patients: 22% male, comparison group: 40% male) and excluding female subjects receiving estrogen replacement therapy from study participation.

Although radiolabeled metabolites of [18F]altanserin appear to cross the blood-brain barrier, these metabolites have been demonstrated to have no significant specific binding to the 5-HT$_{2A}$ receptor in vivo and, therefore, contribute to free and nonspecifically bound radioactivity concentration only (31, 34). These metabolites have been well characterized and do not appear to confound the interpretation of specific binding measures obtained by using the Logan graphical analysis (31). We have also previously shown (19) that age does not affect the rate of metabolism of [18F]altanserin over the 90 minutes after injection.

Since binding potential may reflect changes in receptor density ($B_{\text{max}}$) and/or receptor affinity ($K_D$), abnormalities in either or both measures may contribute to the finding of a difference or, alternatively, a lack of difference in regional binding potential between study groups. However, most postmortem binding assays of 5-HT$_{2A}$ receptor ligands in the brains of suicide victims (3) and Alzheimer’s disease patients (51, 52) have shown abnormal $B_{\text{max}}$ values and normal $K_D$ values. Therefore, it is likely that the low specific binding of [18F]altanserin in several brain regions is the result of a corresponding loss of 5-HT$_{2A}$ receptors, as similarly suggested by Blin et al. (12), who conducted a PET study using [18F]setoperone.

This study addressed our hypothesis—based on prior findings of much lower than normal [18F]altanserin binding in older subjects (19) and controversial postmortem and neuroendocrine evidence for 5-HT$_{2A}$ receptor abnormalities in depressive illness (3, 11, 53, 54)—that specific 5-HT$_{2A}$ receptor binding may be even lower in elderly individuals who suffer from depression. Our data, however, indicate no difference in specific binding of [18F]altanserin in selective brain regions between elderly depressed patients and elderly healthy individuals. This finding is consistent with those of several postmortem studies showing no effect of depression on 5-HT$_{2A}$ receptor binding in younger age groups (50, 54–56). Significantly lower than normal 5-HT$_{2A}$ binding in Alzheimer’s disease was observed and is consistent with results from postmortem and prior in vivo studies suggesting specific serotonergic degeneration in Alzheimer’s disease (7, 8, 11). In contrast to the postmortem work by Bowen et al. (11), who showed similar low levels of 5-HT$_{2A}$ receptors in late-life depression and Alzheimer’s disease, this study suggests that the 5-HT$_{2A}$ receptor may be differentially affected in the two disorders.

REFERENCES


