5HT$_{2A}$ Receptor Binding is Increased in Borderline Personality Disorder

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**Background:** Postmortem studies in suicide victims demonstrate an increase in the number of post-synaptic 5-HT$_{2A}$ receptor binding sites in ventral lateral and orbital frontal cortex. Diminished metabolic responses to serotonergic activation are noted in these areas in impulsive subjects with borderline personality disorder (BPD), a group at high risk for suicidal behaviors. We examined 5HT$_{2A}$ receptor binding potential (BP) in impulsive subjects with BPD, with positron emission tomography neuroimaging with [$^{18}$F] altanserin.

**Methods:** Fourteen female subjects with BPD were assessed for Axis I comorbidity, depressed mood, impulsivity, aggression, suicidality, childhood abuse, and compared with 11 healthy female control subjects. The 5HT$_{2A}$ receptor binding was evaluated in prefrontal cortex, anterior cingulate, hippocampus, temporal lobe, occipital cortex, and thalamus. Data were analyzed with Logan graphical analysis and a four-compartment (4C) model.

**Results:** Hippocampal 5HT$_{2A}$ receptor binding was significantly increased in BPD subjects compared with control subjects in both Logan and 4C analyses, covarying for age. Hippocampal BP values were related to comorbid major depressive episode, with highest values found in non-depressed BPD subjects and lowest in healthy control subjects. The BP values were not related to depressed mood, impulsivity, aggression, suicidality, or childhood abuse.

**Conclusions:** 5HT$_{2A}$ receptor binding is increased in the hippocampus of BPD subjects independent of depressed mood, impulsivity, aggression, suicidality, or childhood abuse. Dysregulation of serotonergic function in hippocampus might contribute to affective and behavioral symptoms in BPD.

**Key Words:** [$^{18}$F] altanserin binding, borderline personality disorder, hippocampus

Borderline personality disorder (BPD) is a clinically relevant, high-risk model for the study of suicidal behavior. It is the only psychiatric disorder defined, in part, by recurrent suicidal or self-injurious behaviors and is a contributing factor in over one-third of completed suicides in community surveys (Isomesta *et al.* 1996; Runeson 1989). Among research subjects ascertained for BPD from consecutive inpatients or outpatients, over 70% are suicide attempters at time of initial assessment, with an average of three lifetime attempts (Soloff *et al.* 1994; Zisook *et al.* 1994). With a completed suicide rate of 10% in long-term follow-up, BPD is one of the most lethal of psychiatric disorders, comparable to affective and schizophrenic disorders (Paris and Zweig-Frank 2001).

Borderline personality disorder is also defined, in part, by impulsivity and aggression, traits of temperament that increase the risk of suicidal behavior across diagnoses (Mann *et al.* 1999). Positron emission tomography (PET) studies in impulsive and suicidal subjects with BPD (and other impulsive personality disorders (PDs)) have reported relative hypometabolism compared with healthy control subjects (in areas of prefrontal cortex (PFC) and frontal and temporal cortex (De La Fuente *et al.* 1997; Soloff *et al.* 2003). Hypometabolism, especially in orbital and medial frontal PFC (Brodmann areas [BA] 9, 10, 11), might be related to increased levels of aggression (Goyer *et al.* 1994) or impulsivity (Soloff *et al.* 2003). Subjects with BPD (and other impulsive PDs) also have diminished metabolic responses in orbital and medial PFC and anterior cingulate, frontal, and temporal cortex to pharmacologic challenge with serotonergic agonists such as d- or d,l fenfluramine (FEN) (Siever *et al.* 1999; Soloff *et al.* 2000) or meta-chlorophenylpiperazine (m-CPP) (New *et al.* 2002). In PD subjects ascertained for impulsivity, level of aggression is inversely related to metabolic response to m-CPP in lateral frontal cortex (BA 47) (New *et al.* 2002). Diminished serotonergic regulation in prefrontal areas, especially orbital and medial PFC might decrease response inhibition, increase impulsivity and aggression, and increase the risk of suicidal behavior (Oquendo and Mann 2000, for review).

The FEN-activated PET studies characterize the net metabolic response of serotonergic neurotransmission in the cortex but cannot assess functional response at the level of specific serotonin receptors. Postmortem receptor studies in suicide victims demonstrate an increase in the number of post-synaptic 5-HT2 binding sites in PFC in some but not all studies and reduced density (B max.) of pre-synaptic tritiated-imipramine binding sites on serotonergic nerve terminals, including the pre-synaptic 5-HT transporter binding site (Arango *et al.* 1995, 1997; Mann *et al.* 1986; Stockmeier *et al.* 1997, for review). These postmortem findings are consistent with a hypothesis of decreased net transmission of serotonergic signal in PFC in suicide victims and compensatory post-synaptic upregulation (Mann and Stoff 1997). Increases in 5HT$_{2A}$ receptor number in suicide victims have been reported primarily in the ventral lateral and orbital frontal cortex (Arango *et al.* 1997), although there are also some increases in 5HT$_{2A}$ binding in the dorsolateral PFC. The most pronounced changes are ventral and involve increased binding to 5HT$_{1A}$ and 5HT$_{2A}$ receptors and decreased binding to the serotonin transporter (Mann and Stoff 1997). These areas overlap the ventral areas of PFC, which demonstrate diminished metabolic responses to activation with FEN and m-CPP in non-depressed subjects with BPD (Soloff *et al.* 2000) and other impulsive PDs (New *et al.* 2002; Siever *et al.* 1999).
We conducted in vivo neuroimaging studies of 5HT2A receptor function in impulsive BPD subjects characterized by recurrent suicidal or self-injurious behaviors and considered at high risk for future suicidal behavior. In vivo imaging studies of high-risk subjects have important clinical advantages over autoradiographic study of completed suicides. They allow for prospective, systematic assessment of risk factors such as psychiatric and medical comorbidities, drug exposure, and treatment experience and close matching of gender, race, and age between cases and control subjects. The whole brain may be examined, which is technically difficult in postmortem autoradiography studies (Mann and Stoff 1997). We used [18F] altanserin, a high-affinity 5HT2A antagonist (Biver et al. 1997; Sadzot et al. 1995), which has been used to demonstrate alterations in 5HT2A receptor binding in PET studies of depression (Biver et al. 1997; Mintun et al. 2004), aging (Meltzer et al. 1998; Rosier et al. 1996), eating disorders (Kaye et al. 2001), and gender differences (Biver et al. 1996). To the best of our knowledge, this is the first study of [18F] altanserin binding in subjects ascertained specifically for BPD. The study was restricted to women to avoid potential gender effects.

Methods and Materials

This study was approved by the Institutional Review Board of the University of Pittsburgh. All subjects gave written informed consent. Female subjects were recruited by advertisement from the outpatient clinics of the Western Psychiatric Institute and Clinic (WPIC), from the surrounding community and from among active participants in the PI’s longitudinal studies of BPD. Diagnoses were determined by trained raters with structured interviews. Axis I disorders were diagnosed with the Structured Clinical Interview for DSM III-R (SCID; Spitzer et al. 1988) (DSM III-R was used to preserve continuity with ongoing longitudinal studies). Axis II disorders were diagnosed with the International Personality Disorders Examination (IPDE) (Loranger et al. 1987). The BPD subjects met diagnostic criteria on the IPDE interview, with a lifetime framework, and on the Diagnostic Interview for Borderline Patients–Revised (DIB-R ≥ 8), with a 2-year time frame (Zamarini et al. 1989). To select a highly impulsive sample, BPD subjects were also required to have a maximal scaled score (3) on the Impulse Action Patterns section of the DIB-R. Patients were excluded for a past or current Axis I diagnosis of schizophrenia, schizoaffective disorder, delusional (paranoid) disorder, bipolar I or II disorders, psychotic depression, or organic mood disorder. Control subjects had no current or lifetime Axis I or II diagnoses. Final diagnoses were determined by consensus of raters with all available data, including medical records. Symptom scales obtained 1 week before the scan included the Hamilton Rating Scale for Depression, 24 item format (HamD) (Guy W 1976) and the self-rated Barratt Impulsiveness Scale–Version 11 (BIS) (Barratt and Slaughter 1998). The Brown-Goodwin Lifetime History of Aggression (LHA) (Brown and Goodwin 1986) was obtained by interview at the time of initial assessment. All subjects had a physical examination, were physically healthy, and free of oral contraceptives and psychoactive medication for a minimum of 2 months (range: 2 months–9 years; four BPD subjects were medication naive). All were free of drugs of abuse and alcohol for at least 5 days before the PET scan (range 5–59 days, mean [SD] = 17.5 [14.5] days), with no evidence of alcohol or drug-related withdrawal symptoms at any point in the assessment process. All subjects had a negative urinalysis for drugs of abuse and a negative pregnancy test at the time of the scan. Subjects were requested to eat a low tryptophan breakfast and no caffeine the day of the scan.

A magnetic resonance imaging (MRI) scan was obtained before the PET study for co-registration of PET data. The MRI scans were acquired with a 1.5 Tesla Signa scanner (GE Healthcare, Milwaukee, Wisconsin). A T1-weighted sagittal scout image was obtained for graphic prescription of the coronal and axial images. Three-dimensional gradient echo imaging (Spooled Gradient Recalled Acquisition (SPGR)) was performed in the coronal plane (repetition time = 25 msec, echo time = 5 msec, mutual angle = 40°, field of view = 24 cm, section thickness = 1.5 mm, number of excitations [NEX] = 1, matrix size = 256 × 192 pixels) to obtain 124 images covering the entire brain. Additionally, a double echo-spin echo sequence was used to obtain T2 and proton weighted density images in the axial plane to screen for neuroradiological abnormalities.

The PET study was conducted in the University of Pittsburgh Medical Center PET Facility. All subjects were scanned on an ECAT HR+ PET scanner (CTI PET Systems, Knoxville, Tennessee) in two-dimensional imaging mode, septa extended, with 63 image planes acquired over a 152-mm axial field-of-view. The 5HT2A receptor antagonist, [18F] altanserin, was synthesized according to previously described methods (Lemaire et al. 1991; Price et al. 2001a, 2001b). A supplemental [15O]water PET study was performed before the [18F] altanserin study to assess any possible influences of blood flow (or perfusion) upon the observed [18F] altanserin kinetics. The PET emission data were corrected for deadtime, attenuation, radioactive decay, and scatter. The PET data were reconstructed with filtered back-projection. The final reconstructed PET image resolution was approximately 6.5 mm (transverse and axial).

Subjects were placed in a recumbent position, and a short 21-gauge plastic catheter was inserted into either the left or right (non-dominant hand) radial artery under local anesthesia. An intravenous line was placed in an antecubital vein and infused with normal saline to keep open. Subjects were positioned in the scanner with the head oriented approximately parallel to the canthomeatal line to include imaging from vertex through cerebellum. A softened thermoplastic facemask with generous holes for eyes, nose, mouth and ears was fitted closely around the head and attached to the head holder to minimize subject motion. A 10-min transmission scan was performed for attenuation correction with rotating 68Ge/68Ga rods. At the end of the transmission scan, 40–50 mCi of [15O]water was injected as an intravenous bolus, and scanning was performed over 3 min. The [18F] altanserin was administered as a slow bolus (20-sec bolus, 10 mCi, high specific activity (> 1.0 Ci/μmol) approximately 20 min after the end of the [15O]water study. A 90-min dynamic PET acquisition began at injection along with arterial blood sampling for the determination of the arterial input function (Bailer et al. 2004).

For each subject, the PET data were co-registered to the MRI data set with an automated algorithm for image alignment and reslicing (Minoshima et al. 1992, Woods et al. 1993). Region-of-interest (ROI) sampling of the PET data was performed on the basis of the co-registered SPGR MR ROIs. Eight ROIs were sampled on the basis of prior reports of functional or structural abnormalities in BPD compared with control subjects, suggesting involvement in borderline psychopathology. In the prefrontal cortex, three ROIs were sampled, including: the medial orbital frontal cortex inferiorly (MOF: BA 11), the medial frontal cortex superiorly (MFC: BA 9/10), and the lateral orbital frontal cortex (LOF: BA 45/47). The MOF includes the cortex within the gyrus rectus, whereas the MFC

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samples the superior frontal gyrus and medial portion of the medial frontal gyrus at the level of the superior-most section through the body of the lateral ventricles. The anterior cingulate (ANC: BA 32) and its subdivisions were sampled: the pregenual cingulate (PRG: BA 24/32, anterior to the anterior-most part of the corpus callosum), and the subgenual cingulate (SUG: BA 25, inferior to the genu of the corpus callosum). As previously noted, the prefrontal ROIs and anterior cingulate might be important in regulation of impulsivity and aggression in BPD and other impulsive PDs (New et al. 2002; Siever et al. 1999; Soloff et al. 2000, 2003). The subgenual cingulate is strongly implicated in depressive illness, which is commonly comorbid with BPD (Drevets et al. 1997). The hippocampus (HIP) was sampled as a discrete ROI and as part of a larger area in medial temporal cortex (MTC), which included the hippocampal-amygdala complex. Structural and functional MRI (fMRI) studies in BPD subjects demonstrate abnormalities in HIP and amygdala compared with healthy control subjects (reviewed in subsequent text). Two control regions were sampled: the occipital cortex (OCC: BA 18), and the thalamus (THL), representing cortical and limbic regions not involved in our hypothesis. The cerebellum (CER) was defined as a reference region, emphasizing cerebellar hemisphere gray matter at the level of the inferior portion of the fourth ventricle. Because [18F] altanserin binding is not entirely absent in cerebellum, CER distribution volumes (DVs) were compared between groups (Dwivedi and Pandey 1998; Staley et al. 2001). ROIs were hand drawn on the MR images according to anatomic landmarks and transferred to the co-registered summed PET images for regional sampling. Drawing of ROIs was done blind to diagnosis. For each ROI, BP values were analyzed for left and right hemispheres to identify lateralized effects and as a pooled sample.

The ROIs were applied to the dynamic PET images to generate regional time-activity curves that were analyzed with either the Logan or compartmental analyses. Measures of cerebral blood flow were obtained from the [15O] water data with a one-tissue compartment model, as previously described (Price et al. 2002). The [18F] altanserin PET data were analyzed with two types of arterial-based methods. First, the linear Logan graphical method was applied for the 12–90-min interval (Bailer et al. 2004; Logan et al. 1990; Meltzer et al. 1998; Smith et al. 1998). Second, a supplemental 4-compartment (4C) model with 3-tissue compartments and 6 kinetic parameters (K1–k6) was also applied (Price et al. 2001b). The 4C model provides a nonlinear description of the in vivo kinetics that is more comprehensive in its account for nonspecific uptake (e.g., radiolabeled metabolites), relative to the Logan method. The 4C method, however, generally yields parameter estimates that are more variable than those obtained via linear methods. The 4C results were therefore secondary measures used to substantiate the Logan results. For [18F] altanserin, the Logan BP was found to be a good outcome measure, although it is systematically biased relative to the 4C BP (Price et al. 2001b).

For the Logan analysis, the regional DV value was used to determine BP, where BP = DVR-1 and DVR is the ratio of the DV value for a ROI to the DV for the reference region, the cerebellum (Lammertsma and Hume 1996). For the 4C analysis, BP was determined as the k3/k4 ratio (Koepppe et al. 1991; Mintun et al. 1984, 2004; Price et al. 2001b) that is equivalent to DVR-1. The nonspecific 4C kinetic parameters (k5 and k6) were determined in the cerebellum and constrained to the cerebellar values for the regional 4C curve fits. The BP measures were corrected for partial volume effects due to cerebral spinal fluid dilution with MR-based correction factors that varied from 0 to 1 (no dilution) that were determined with a routinely applied method (Meltzer et al. 1999).

The SPSS version 13.0 was used for statistical analyses (SPSS, Chicago, Illinois). Normality and homogeneity of variance were tested with the Kolmogorov-Smirnov one sample test and Levine's test, respectively. Log (ln) transformation was applied where needed. Demographic and symptom data were compared between groups by t tests and χ2 tests as appropriate. As a first exploratory analysis, effects of diagnostic group (BPD, healthy control subjects [HC]) on BP values were tested by analysis of covariance (ANCOVA) for each pooled ROI, with age as covariate. Threshold criterion for further analysis was set at p < .1, without Bonferroni correction. Linear regression was used to test the relationship of clinical variables to the BP values in the remaining ROIs, with age and diagnostic group as additional independents in each model. The predefined clinical variables included: current major depressive episode (MDE); suicide attempter status; lifetime number of suicide attempts; and childhood history of sexual or physical abuse, examined separately. Because 12 of 14 BPD subjects were found to be past suicide attempters, the regression of attempter status on BP values was restricted to 12 BPD attempters and 11 healthy control subjects, with age the only other independent variable. The relationship of the three symptom scales (HamD, BIS, LHA) to BP values were examined by Pearson correlation coefficients and regression models (with age, diagnostic group, and individual symptom scales as independent variables and BP values for each ROI as dependent variables). The effects of the symptom scales on the relationship between diagnostic group and BP values were tested by ANCOVA, with age and individual symptom scales as covariates.

**Results**

Fourteen female BPD subjects were compared with 11 healthy control subjects (HC). The total sample had an age range of 19–46 years. The mean (SD) age of BPD subjects was 27.7 (8.2) years, not significantly different from control subjects (27.3 [10.6] years) (Table 1). The two groups did not differ significantly in mean height, weight, basal metabolic index (BMI), or days from onset of menstrual cycle.

Comorbidity in the BPD sample included five subjects with a current Axis I SCID diagnosis of MDE, three with a current dysthymic disorder, and one with depression not otherwise specified (NOS). Nine subjects had a past (lifetime) diagnosis of MDE. Twelve of 14 BPD subjects (85.7%) had a past history of suicide attempts, with a mean (SD) of 2.5 (2.1) attempts/person. Seven subjects met criteria for a current substance use disorder, with no evidence of withdrawal before the PET scan: two as dependence (alcohol), and five as abuse (alcohol [one], cannabis [two], alcohol plus cannabis [one], stimulant [one]). For the two subjects with an alcohol dependence diagnosis, the period of abstinence before scan was 8 and 13 days, respectively, with no evidence of withdrawal. Twelve subjects met criteria for a lifetime diagnosis of substance use; only 1 BPD subject was drug naive. Five BPD subjects had childhood histories of sexual abuse; six had physical abuse. Compared with healthy control subjects, BPD subjects had significantly more depressed mood (HamD), impulsivity (BIS), and lifetime aggression (LHA) (Table 1). There were no significant correlations between measures of impulsivity and aggression, although both were significantly related to depressed mood [BIS: r = +.58, n = 25, p = .003; LHA: r = +.53, n = 25, p = .006].
Table 1. Clinical Characteristics and BP Values in BPD and Control Subjects

<table>
<thead>
<tr>
<th>ROI</th>
<th>BPD (mean, SD)</th>
<th>Control (mean, SD)</th>
<th>t, df, p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIP</td>
<td>.44 (.14)</td>
<td>.77 (.27)</td>
<td>.31 (.12)</td>
</tr>
<tr>
<td>HIP-rt.</td>
<td>8.27, .009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIP-lt.</td>
<td>5.19, .03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTC</td>
<td>.44 (.12)</td>
<td>.70 (.20)</td>
<td>.38 (.10)</td>
</tr>
<tr>
<td>MTC-rt.</td>
<td>5.44, .03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTC-lt.</td>
<td>3.35, .08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOF</td>
<td>1.61 (.39)</td>
<td>2.28 (.56)</td>
<td>1.48 (.32)</td>
</tr>
<tr>
<td>LOF-rt.</td>
<td>2.73, .11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOF-lt.</td>
<td>3.35, .08</td>
<td></td>
<td></td>
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<tr>
<td>OCC</td>
<td>1.45 (.36)</td>
<td>2.20 (.47)</td>
<td>1.30 (.26)</td>
</tr>
<tr>
<td>OCC-rt.</td>
<td>6.03, .02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCC-lt.</td>
<td>8.31, .009</td>
<td></td>
<td></td>
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<tr>
<td>CER_dv</td>
<td>1.21 (.17)</td>
<td>1.13 (.25)</td>
<td>1.30, .27</td>
</tr>
</tbody>
</table>

BP, binding potential; BPD, borderline personality disorder; HamD, Hamilton Rating Scale for Depression, 24 item format; BIS, Barratt Impulsiveness Scale-Version 11; LHA, Brown-Goodwin Lifetime History of Aggression; ROI, region-of-interest; HIP, hippocampus; MTC, medial temporal cortex; LOF, lateral orbital frontal cortex; OCC, occipital cortex; CER_dv, cerebellar distribution volume.

*Logan BP: BPD vs. control subjects, analysis of covariance (ANCOVA) with age as covariate, df = (1,24).

**k3/k4: BPD vs. control subjects, ANCOVA with age as covariate: F(1,24) = 4.46, p = .046.

There were no significant differences between groups in nonspecific binding, measured by CER DV (Table 1), or in the MR-determined cerebrospinal fluid (CSF) correction factors. The contribution of CSF partial volume effects to the regional values was generally minimal, because the average correction factors for the ROIs ranged from .76 to 1.00. The lowest average correction factors were determined for the LOF (.86 to .89) and MFC regions (.76). There were no significant differences between groups in blood flow values for any ROI. Metabolite levels sampled at 2, 10, and 30 min after injection were significantly greater in healthy control subjects at each time compared with BPD; however, at 60 and 90 min after injection, there were no differences between groups in metabolite levels.

In all 10 of the pooled ROIs, altanserin binding was greater in BPD compared with control subjects (Figure 1). Diagnostic group (BPD vs. HC) had a significant effect on altanserin binding (with age covaried) in the HIP and OCC, with trends (p < .1) in MTC and LOF (Table 1). Age was a significant covariate (p < .001) in each of these contrasts. When BP values were compared by hemisphere, the effect of diagnostic group on HIP was significant for both left and right hemispheres although more robust in the left. Similarly, BP values were greater in BPD subjects compared with control subjects in both left and right OCC. In the MTC (which includes both HIP and amygdala), the near-significant effect of diagnostic group on altanserin binding in the pooled sample (p = .06) seemed to be attributable to the left hemisphere, perhaps reflecting the robust finding in HIP on the left. Analysis of BP values in left and right LOF revealed nonsignificant effects (Table 1). There were no significant laterolized effects of diagnostic groups on altanserin binding in any of the other ROIs. To reduce multiple comparisons, all further analyses were restricted to pooled samples of HIP, OCC, MTC, and LOF.

We examined the effects of MDE on altanserin binding in the 4 ROIs with ANCOVA, covarying for age. A significant effect for MDE was found on BP values in the HIP [F(2,24) = 9.10, p = .001] but not in LOF, MTC, or OCC. Non-depressed BPD subjects had the highest mean (± SD) hippocampal BP values (.46 ± .15), followed by depressed BPD subjects (.39 ± .12) and healthy control subjects (.31 ± .12). The difference in hippocampal BP values was significant between the 9 non-depressed BPD subjects and 11 healthy control subjects [F(1,19) = 14.90, p = .001] and between the 9 non-depressed and 5 depressed BPD subjects [F(1,13) = 10.34, p = .008] but not between the depressed and control subjects, with age covaried in each analysis.

When analyses were restricted to 12 BPD suicide attempters compared with healthy control subjects, Logan BP values were significantly greater for BPD attempters in HIP [F(1,12) = 13.84, p = .001], MTC [F(1,12) = 4.55, p = .046], and OCC [F(1,12) = 5.88, p = .025], with trend significance in LOF [F(1,12) = 3.49, p = .081], each covaried for age. There were no significant relationships between BP values and childhood sexual or physical abuse or lifetime number of suicide attempts in any of the four ROIs.

The BP values in each of the four ROIs were highly intercorrelated [with Pearson coefficients ranging from r = .72 to r = .88, all p < .001, for n = 25]. Age was significantly and inversely related to altanserin binding in each of the four ROIs, in both BPD and control groups [BPD: r = -.68 to r = -.88, all p < .01; Control: r = -.64 to r = -.92, all p < .05]. There were no significant correlations between BP values and measures of depressed mood (HamD), impulsivity (BIS), or aggression (LHA). Increased binding of altanserin in HIP among subjects with BPD compared with control subjects was statistically independent of depressed mood, impulsivity, or aggression in separate analyses, each covaried for age.

The 4C BP was in agreement with the Logan BP with respect to increased BP values in HIP among BPD women (.77 ± .28) relative to control subjects (.61 ± .23, F(1,24) = 4.32, p = .046,
Discussion

This first study of altanserin binding in subjects ascertained specifically for BPD produced unexpected results. Differences between groups reflected increased binding in BPD compared with control subjects in all ROIs. Among suicide attempters, BP values were significantly greater in HIP, MTC, and OCC, compared with healthy control subjects, with trend significance in lateral orbital frontal cortex. However, the most robust finding, demonstrated with both Logan and 4C analytic models, was of increased altanserin binding in the HIP, especially among non-depressed BPD subjects, compared with normal control subjects.

The BP values in the prefrontal cortex (e.g., LOF) in BPD subjects, although in the expected direction, fell short of statistical significance in comparison with control subjects. Normative studies of altanserin binding indicate that most $5\text{HT}_{2A}$ binding in healthy subjects is in areas of the frontal and prefrontal cortex (i.e., superior medial frontal cortex, dorsolateral and ventral lateral PFC) and OCC but very little in the HIP or amygdala (Adams et al. 2004).

Increased altanserin binding suggests decreased serotonergic agonism and compensatory upregulation of post-synaptic $5\text{HT}_{2A}$ receptor number or a functional increase in $5\text{HT}_{2A}$ receptor responsiveness. In preclinical studies, agonism at the $5\text{HT}_{2A}$ receptor is associated with increases in dopaminergic function and increased aggression (e.g., disinhibited dominance aggression in canines is associated with increased cortical uptake of the $5\text{HT}_{2A}$ receptor radioligand $^{123}\text{I}-\text{IR91150}$) (Peremans et al. 2003). Antagonism at the $5\text{HT}_{2A}$ receptor reduces aggression. Increased hippocampal $5\text{HT}_{2A}$ receptor binding has not been noted previously in studies of BPD patients or in potentially related studies of suicide attempters, completers, or untreated depressed patients.

Meyer et al. (2003) conducted an [$^{18}$F] setoperone study in subjects ascertained for chronic suicidal ideation and self-harm behaviors or major depressive disorder (MDD), assessing $5\text{HT}2$ binding in predefined ROIs including: middle frontal gyrus, lateral orbital frontal cortex, posterior MTC, and rostral anterior cingulate. Statistical parametric mapping (SPM) was used to provide whole brain analysis. [$^{18}$F] setoperone is an antagonist with affinity for $5\text{HT}_{2A}$, $5\text{HT}_{2C}$, and D2 receptors. Although not specifically recruited for BPD, all self-harm subjects also met criteria for BPD, with or without MDD. No significant differences were found between self-harm and control subjects on $5\text{HT}2$ binding in any ROI. Among subjects with MDD (with and without BPD), a positive correlation was noted between $5\text{HT}2$ binding potential and scores on a Dysfunctional Attitude Scale but not on overall severity of depressive symptoms (Ham-D). Administration of d-fenfluramine to control subjects (only) in this study acutely diminished dysfunctional attitudes, suggesting an inverse relationship between dysfunctional attitudes and level of serotonergic agonism.

Audenaert et al. (2001) conducted a small sample study of recent suicide attempters of diverse diagnoses, with single-photon emission tomography (SPECT) and $^{123}\text{I}-\text{I}-\text{IR91150}$, a $5\text{HT}_{2A}$ receptor antagonist. They found decreased binding potential of $5\text{HT}_{2A}$ receptors in attempters compared with control subjects in frontal cortex. Predefined ROIs included areas of prefrontal and frontal cortex but not HIP. A “frontal binding index” was inversely correlated with measures of hopelessness and harm avoidance (on Cloninger’s Temperament and Character Inventory) and directly with personality dimensions of self-directedness and cooperativeness. Postmortem studies of depressed suicides (Cheetham et al. 1988; Rosel et al. 2000) and altanserin-PET studies of untreated depressed patients (Mintun et al. 2004) have also reported a decrease in the number of $5\text{HT}_{2A}$ binding sites and decreased altanserin binding in HIP of depressed compared with control subjects. In our sample, altanserin binding in HIP was significantly less in depressed compared with non-depressed BPD subjects but not different from healthy control subjects, who had the lowest hippocampal BP values. We were unable to relate increased altanserin binding to impulsivity or aggression, which are personality traits inversely related to measures of serotonergic agonism in suicidal subjects, including BPD and other impulsive PDs (Oquendo and Mann 2000). Altanserin binding was also independent of lifetime number of suicide attempts.

The HIP has received little attention in functional imaging studies of patients with BPD. Most PET studies, although not all, find no metabolic differences in HIP in BPD compared with control subjects, although analytic methods such as SPM or multiple temporal ROIs could have detected differences (De La Fuente et al. 1997; Goyer et al. 1994; New et al. 2002; Siever et al. 1999; Soloff et al. 2000, 2003). In one exception, Juengling et al. (2003) found decreased glucose uptake at rest in (left) HIP in BPD women compared with healthy control subjects.

Functional studies that pair provocative emotional stimuli with PET or MRI imaging, have demonstrated aberrant function in HIP and/or associated amygdala in BPD subjects compared with healthy control subjects. Schmahl et al. (2003) paired a psychodynamically relevant “abandonment script” with an [$^{15}$O] water study of cerebral blood flow (CBF) and found decreased regional CBF (rCBF) in BPD subjects compared with control subjects in (right) HIP and amygdala. Decreased rCBF in BPD subjects was also noted in areas of PFC (medial frontal), anterior cingulate, inferior frontal, superior and middle temporal cortex. In an fMRI study, Herpertz et al. (2001) found increased blood oxygen level dependent (BOLD) fMRI signal in amygdala (bilaterally) in BPD subjects compared with control subjects during exposure to standardized emotionally aversive slides. Similarly, Donegan et al. (2003) found that pictures of emotional expression (Ekman faces) produced increased levels of (left) amygdala activation in BPD subjects compared with control subjects.

The HIP has received much greater attention in structural MRI studies of BPD patients, where an association has been established between childhood histories of abuse and hippocampal volume loss (Brambilla et al. 2004; Driessen et al. 2000; Rusch et al. 2003; Schmahl et al. 2003; Tebartz van Elst et al. 2003). Women with BPD who have childhood histories of abuse demonstrate significant volume loss in both HIP and amygdala and an inverse relationship between duration of childhood traumatization and hippocampal volume (Driessen et al. 2000). In an expanded sample, including all current study subjects, we found diminished concentration of grey matter in medial temporal lobe (in the parahippocampus, uncus, and...
amygdala), bilaterally, in BPD women compared with control subjects with voxel-based morphometry. Within the BPD sample, a subset of sexually abused women had decreased grey matter concentrations in (left) MTC compared with non-abused women (Soloff et al. 2006).

Hippocampal volume loss is not specific to BPD but has also been reported in subjects with chronic posttraumatic stress disorder, remitted and current MDD, especially with histories of childhood abuse (Bremner et al. 2003; Sheline et al. 1996, 2000; Vythilingham et al. 2002). Hippocampal volume loss in these clinical settings might be the result of chronic stress, HPA dysfunction, hypercortisolism, and the neurotoxic effects of cortisol on hippocampal neurons, including diminished brain-derived neurotrophic factor (see Bremner 1999; Sapolsky 2000; Sheline 2000, for reviews). Diminished serotonergic function in HIP is also noted in animal models of stress. Mintun Sheline 2000, for reviews). Diminished serotonergic function in derived neurotrophic factor (see Bremner 1999; Sapolsky 2000; clinical settings might be the result of chronic stress, HPA Vythilingham childhood sexual abuse and 5HT2A binding in the HIP. A larger sample, stratified by severity of abuse, would be needed to test these relationships.

The functional significance of increased 5HT2A binding in HIP is unclear. On the basis of available data, we suggest two preliminary hypotheses, one relating to affective and behavioral instability, the other to dysfunctional attitudes (Deakin 2003, for review). The HIP is involved in declarative, episodic, and working memory function in man; processes sensory inputs; and “updates” associative memory networks. It plays a critical role in attentional monitoring of the current state of both external and internal sensory worlds, including adaptive responding to current and anticipated threat (Wall and Messier 2001). Through extensive reciprocal connections to the orbitomedial PFC, the HIP contributes to associative memory function in the regulation of emotional responding and response inhibition. Dysregulation of serotonergic functions in these circuits might contribute to affective instability and behavioral impulsivity.

Diminished function in serotonergic circuits in HIP might also be associated with low self-esteem, hopelessness, and pessimism (Deakin 2003). These symptoms mirror the “dysfunctional attitudes,” noted by Meyer et al. (2003) to be associated with decreased serotonergic agonism and increased 5HT2 binding in patients with MDD (with and without BPD). Dysfunctional attitudes are “negatively biased views of oneself, the world and the future” and are highly prevalent in patients with BPD, independent of depressed mood (Meyer et al. 2003; O'Leary et al. 1991). In the Meyer et al. (2005) study, scores on the Dysfunctional Attitude Scale were not related to depressed mood (HamD) and improved in control subjects given d-fenfluramine. Among our BPD subjects, BP values in HIP are highest in non-depressed subjects and independent of HamD scores. Diminished serotonergic function in HIP might mediate dysfunctional attitudes in BPD, which, in turn, might influence affective and behavioral responses at times of stress, including suicidal behavior. These hypotheses are complementary and interactive. Further research is needed to assess the hypothesized relationships between increased 5HT2A binding, dysfunctional attitudes, and impulsive and suicidal behavior in BPD.

Limitations

Altanserin binding is strongly and inversely related to age (Meltzer et al. 1998). Large differences in mean age of samples might produce variation in results between studies, although age effects on altanserin binding are statistically controlled within studies. This was a study restricted to female subjects. Gender effects on binding to the 5HT2a receptor have been reported by some investigators (Biver et al. 1996) although not others (Meltzer et al. 1998). Estrogen levels might have a modulatory effect on 5HT2a binding (Moses et al. 2000). Differences in gender composition of samples or hormonal status of women within samples can contribute to differing outcomes between studies (e.g., Mintun et al. [2004] studied a mixed gender sample, with an age range of 20–85 years, without regard to menstrual status).

[18F] altanserin is not completely selective and binds to 5HT2c as well as 5HT2A receptors. The 5HT2c receptor is expressed only to a small degree in the cortex compared with the 5HT2A (Lemaire et al. 1991; Mintun et al. 2004); however, it is not negligible in HIP and potentially contributes to our BP findings. Altanserin has a 20-fold greater affinity for the 5HT2A receptor compared with the 5HT2c. 5HT2A binding would account for > 95% of radiotracer binding in cortex if the two receptors were present in equal concentrations (Tan et al. 1997, 1999). Radiolabeled metabolites of [18F] altanserin cross the blood brain barrier and complicate quantification of BP. These metabolites have been demonstrated to have no significant specific binding to the 5HT2A receptor in vivo and therefore contribute to free radioligand concentration and nonspecific binding only (Mason et al. 1997; Meltzer et al. 1998; Price et al. 2001b).

Substance use disorders are highly prevalent in BPD and can confound studies of serotonergic function. All substance users in this study had a “recreational” pattern with no evidence of withdrawal before PET scan. Use of psychoactive medications can also affect serotonergic function weeks after discontinuation. Subjects with a past history of psychoactive drug use were med-free for at least 2 months before the PET scan. We found no subjects with outlier BP values across ROIs or evidence that distributions of BP values were skewed by a few individuals.

Analysis of the [15O] water data did not reveal differences between groups in any ROI. This was disappointing, because [18F]-fluorodeoxyglucose(FDG)-PET studies in BPD subjects have repeatedly demonstrated hypometabolism in areas of prefrontal, frontal, and temporal cortex (reviewed in preceding text), and a relationship is presumed between CBF and glucose use. Few studies have assessed CBF in subjects ascertained for BPD. Schmahel et al. (2003) measured CBF during recitation of a personalized “abandonment text” (compared with a neutral script) in BPD women with histories of childhood sexual abuse and found decreased perfusion in (right) HIP, amygdala, and areas of prefrontal, frontal, and middle temporal cortex. Differences in sample selection and method might account for differing results between studies.

Finally, the modest sample sizes in this exploratory study might have insufficient power to detect small group differences in rCBF or altanserin binding. The relationship between comorbidity and altanserin binding in BPD will need to be re-assessed with larger numbers. We found, contrary to Mintun et al. (2004), no significant differences in BP values between BPD subjects with comorbid MDE and normal control subjects. We also found no significant effects of HamD scores on BP values in any ROI or correlations between HamD and BP values. In this exploratory study, we were concerned with sampling multiple areas implicated in the regulation of mood, impulsivity, and
agression in BPD yet limiting the number of ROIs. Correction for multiple comparisons—not appropriate in this first exploratory study—will be important in confirmatory analyses on larger samples. Future studies will seek correlations between alterations in the prefrontal cortex of suicide victims. Brain Res 688:121–133.


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