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Serotonin-1A Receptor Imaging in Recurrent Depression: Replication and Literature Review

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Abstract

Introduction—Serotonin 1A receptor (5-HT_{1A}R) function appears decreased in primary major depressive disorder (MDD) based upon physiological responses to 5-HT_{1A}R agonists *in vivo* and 5-HT_{1A}R receptor binding in brain tissue *post-* or *antemortem*. We previously assessed 5-HT_{1A}R binding potential (BP) in depression using PET and [*carbonyl*-¹¹C]WAY-100635, and demonstrated reduced 5-HT_{1A}R BP in the mesiotemporal cortex (MTC) and raphe in depressives with primary, recurrent, familial mood disorders (n=12) versus controls (n=8)[1]. These findings were replicated by some, but not other studies performed in depressed samples more generally selected using criteria for MDD. In the current study we attempted to replicate our previous findings in an independent sample of subjects selected according to the criteria for primary, recurrent depression applied in our prior study.

Methods—Using PET and [*carbonyl*-¹¹C]WAY-100635 the 5-HT_{1A}R BP was assessed in 16 depressed subjects and 8 healthy controls.

Results—Mean 5-HT_{1A}R BP was reduced 26% in MTC (p<0.005) and 43% in raphe (p<0.001) in depressives versus controls.

Conclusions—These data replicated our original findings, which showed BP reduced 27% in MTC (p<0.025) and 42% in raphe (p<0.02) in depression. The magnitudes of these reductions in 5-HT_{1A}R binding were similar to those found *post mortem* in 5-HT_{1A}R mRNA concentrations in hippocampus in MDD [2] and in 5-HT_{1A}R binding capacity in the raphe in depressed suicide victims [3]. Disagreement exists within the literature, however, regarding the presence and direction of 5-HT_{1A}R binding abnormalities in depression, which may be explained in some cases by differences in anatomical location (e.g., [4]) and in others by pathophysiological heterogeneity within MDD (e.g., some depressives hypersecrete cortisol, which would be expected to down-regulate 5-HT_{1A}R expression[2]). Antidepressant drug treatment does not alter these abnormalities in 5-HT_{1A}R binding [5,6], but may compensate for blunted 5-HT_{1A}R function by increasing post-synaptic 5-HT_{1A}R transmission [7].

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Keywords

PET; major depressive disorder; bipolar disorder

The central serotonergic system has received great interest in depression research, based initially on observations that selective serotonin reuptake inhibitors (SSRI) exert antidepressant effects, and that most other antidepressant drugs also increase serotonin (5-HT) transmission. This effect was thought to compensate for deficient serotonergic function in major depressive disorder (MDD), since remitted MDD subjects who are unmedicated or are being treated with SSRI agents experience depressive relapse under tryptophan depletion (which putatively decreases central serotonergic function (reviewed in [8])). The most promising evidence for a serotonin system deficiency that is compensated by antidepressant pharmacotherapy involves post-synaptic serotonin type 1A receptors (5-HT_{1A}R). Chronic administration of antidepressant drugs with diverse primary pharmacological actions enhances post-synaptic 5-HT_{1A}R function through a variety of receptor pharmacological mechanisms [7,9]. Moreover, *post mortem*, neuroimaging and pharmacological challenge studies of depression have reported abnormalities in the 5-HT_{1A}R density and mRNA expression [2-4,10]. These abnormalities appear to be associated with reduced 5-HT_{1A}R function, as depressed subjects show blunted thermic and endocrine responses to 5-HT_{1A}R agonist challenge (reviewed in [1]).

The development of 5-HT_{1A}R selective PET radioligands has enabled *in vivo* measures of pre- and post-synaptic 5-HT_{1A}R binding in depression. In a previous study we demonstrated that mean 5-HT_{1A}R binding potential (BP) was reduced in the mesiotemporal cortex (MTC) and raphe in unmedicated-depressives relative to controls using PET and [*carbonyl*-¹¹C]WAY-100635[1]. Similar reductions were evident in the parietal and medial occipital/posterior cingulate cortices. These data were consistent with those of Sargent et al [5], who found decreased 5-HT_{1A}R BP, measured using PET and [¹¹C]WAY 100635, in unmedicated depressives relative to controls in the raphe, MTC, insula, anterior cingulate cortex, temporal polar cortex and orbital cortex. Similarly, Meltzer et al.[11] found significantly decreased [¹¹C]WAY-100635 binding in the raphe in elderly depressed patients (n=17) relative to age-matched controls (n=17). Several studies reported that these reductions in 5-HT_{1A}R binding also were evident in currently remitted patients with a history of MDD [5,6,12], suggesting that this abnormality persists across illness episodes in recurrent depression.

Not all PET studies of 5-HT_{1A}R in depression are in agreement, however. Parsey et al[13] found no difference in BP between depressed MDD subjects and controls. Moreover, they reported that in antidepressant drug naïve MDD subjects, the BP values exceeded those of controls. These data contrasted with our own finding that antidepressant naïve cases had similar (or lower) BP than previously treated patients[14], as well as with those of longitudinal studies showing that antidepressant drug treatment exerted no significant effect on the abnormal reductions in BP in MDD [5,6]. Nevertheless, disagreement regarding the presence and direction of abnormalities also exists within the *post mortem* literature (see Discussion), raising the possibility that clinical and pathophysiological heterogeneity within the conditions encompassed by the major depressive syndrome contributes to discrepancies in the results across studies.

Lopez et al[2] hypothesized that the reduced hippocampal 5-HT_{1A}R mRNA found in depressed subjects *post mortem* specifically arose in response to the cortisol hypersecretion associated with MDD, since hippocampal 5-HT_{1A}R mRNA expression is under tonic inhibition by adrenal corticosteroids. In rats and tree shrews hippocampal 5-HT_{1A}R density and mRNA levels decrease in response to corticosterone administration and chronic stress, and increase following

adrenalectomy [15-22]. Adrenalectomy also prevents stress-induced down-regulation of 5-HT_{1A}R expression[2].

The sensitivity for detecting 5-HT_{1A}R abnormalities in depressed samples may thus be enhanced by selecting subjects with a higher likelihood of having glucocorticoid hypersecretion. Imaging data have generally added to a variety of other types of psychobiological information to indicate that, in the absence of other entrance criteria, the DSM-series[23] criteria for MDD by themselves provide low sensitivity and specificity for detecting biological abnormalities. In contrast, depressives with bipolar disorder (BD) or with the MDD (unipolar depression) subtypes of *melancholia* or familial pure depressive disease (FPDD; i.e., *primary* MDD subjects who have first degree relatives with MDD, but not BD, alcoholism or antisocial personality disorder; where *primary* indicates that the depression did not arise in the setting of pre-existing medical or psychiatric disorders) proved more likely to show evidence of limbic-hypothalamic-pituitary-adrenal (LHPA) axis hyperactivity than depressed cases who did not meet criteria for these subtypes [24-28]. Moreover, Lewis & McChesney[29] showed that the mean platelet [³H]imipramine uptake was reduced in BD and FPDD but not in other MDD subtypes, suggesting the former subtypes may more likely manifest serotonergic dysfunction. Thus, to enhance the likelihood of detecting abnormalities in 5-HT_{1A}R BP in depression our initial PET study [1] selected an “enriched sample” of depressed subjects who had a primary mood disorder and also fell within either the FPDD or BD spectrum categories.

This previous study assessed 5-HT_{1A}R binding in 12 depressives with primary, recurrent depression, of whom 8 had MDD, and 4 had BD [1]. Of the MDD subjects, 4 met criteria for FPDD, while 4 had a first degree relative with BD, and thus were considered within the bipolar spectrum of affective illness (the offspring or monozygotic twin of an index case with BD can develop MDD, BD or schizoaffective disorder, suggesting that these conditions reflect the inheritance of a genotype which can be expressed as a spectrum of phenotypes of differing severities).[30] While differences in 5-HT_{1A}R binding with respect to controls were evident when the 8 bipolar spectrum cases (BD subjects plus MDD subjects with bipolar relatives) were considered alone, the BP values in the small sample of 4 FPDD subjects did not differ significantly from controls when considered alone. Thus, in the current study we attempted to replicate our previous findings using an *independent* sample of depressed subjects with primary, recurrent mood disorders which included sufficient numbers of MDD cases within the FPDD or melancholic subtypes to permit extension of these findings to an enriched sample of unipolar depressives.

Methods

Depressed subjects (n=16; 10 female; mean age 32±10 years, range= 19 to 51 years) met DSM-IV criteria[23] for primary, recurrent MDD or BD, and had experienced depression onset prior to age 40 years. Fourteen subjects met DSM-IV criteria for MDD and two had BD, most recent episode depressed. Based upon family history, 3 of the MDD cases had a first degree relative with BD. Of the 11 MDD cases who did not have first degree relatives with BD, 7 were included for meeting FPDD criteria (of whom 4 also met melancholic subtype criteria) and 4 for meeting DSM-IV melancholic subtype, but not FPDD, criteria. Exclusion criteria included medical or neurological illnesses, MRI evidence of neuromorphological abnormalities, suicidal intent, substance abuse within 1 year, lifetime history of substance dependence (other than nicotine), and exposure to psychotropic medications within 3 weeks (8 weeks for fluoxetine).

Healthy controls (n=8; 4 female; mean age 32±12 years, range=18 to 50 years) met the same exclusion criteria and did not meet criteria for past or current psychiatric disorders.

Depression severity was rated using the Hamilton Rating Scale for Depression (HRSD [31]), and anxiety severity using the Spielberger State-Trait Anxiety Inventory (State; STAI) [32]. The plasma cortisol concentrations during the stress related to scanning (late morning to early afternoon for all subjects) was measured as described previously [1,33].

None of the subjects in the current study participated in our previous study[1]. The depressed subjects were recruited from the out-patient psychiatric services of the University of Pittsburgh Medical Center (UPMC). All subjects provided written informed consent as approved by the UPMC Institutional Review Board.

Data Acquisition

A dynamic emission scan (29 frames of increasing length over 60 min) was acquired following i.v. bolus administration of 10 to 20 mCi of high specific activity [*carbonyl*- ^{11}C] WAY-100635], synthesized using a modification of the McCarron et al [34] method. Images were acquired using a Siemens/CTI HR+ (63 contiguous slices over 15.2 cm) in 3D mode [FWHM resolution = 5 ± 0.5 mm transverse and 4.5 ± 0.5 mm axially]. A Neuro-insertTM (CTI PET Systems, Knoxville, TN) was locked into the scanner gantry to reduce random coincidences. Images were reconstructed using a Hanning window with cut-off = Nyquist frequency, resulting in an estimated (including the effect of scatter) true image FWHM resolution of 7.1 mm transverse and 6.7 mm axially.

MRI scans were obtained using a 1.5 T GE Signa Scanner and a 3-D spoiled gradient recalled (SPGR) sequence optimized for delineating gray matter/white matter/CSF boundaries.

Data Analysis

PET and MR images were aligned using AIR [35]. Because power was relatively low in this small sample size, hypothesis-testing was limited to the MTC and raphe. The MTC region-of-interest (ROI) was defined by manual tracing around the hippocampus, amygdala, and adjacent parahippocampal and periamygdaloid cortex bilaterally using ImageToolTM (CTI PET Systems, Knoxville, TN) in the 6 to 7 planes where both amygdala and hippocampus were evident, as described in Drevets et al.[1](Figure 1). The raphe ROI was centered over the raphe nuclei located within the midbrain and rostral-most slices of the pons, collectively evident in [^{11}C]WAY-100635 images because of their very high 5HT_{1A}R density relative to that of surrounding tissues [36]. The raphe is inadequately visualized in MR images for boundary tracing, so this ROI was defined directly on PET images (Figure 1). The midbrain raphe and upper pons were selected to emphasize measures from the dorsal and median raphe nuclei, which innervate the forebrain. These relevant horizontal sections were identified in the co-registered MRI slices, and circular ROI (5 mm radius) were centered over the brainstem area of high tissue radioactivity in each slice as described in Drevets et al.[1]. The diameter of this ROI was larger than that of the actual raphe to accommodate the blurring of the raphe 5-HT_{1A}R-specific signal in PET images and reduce the effects of possible position differences in the raphe signal due to movement between frames.

The reference region for measuring free and nonspecifically bound radioligand concentrations was the cerebellar cortex. The cerebellum is most suitable as the reference tissue because it is nearly devoid of 5-HT_{1A}R protein and mRNA, and is large enough that ROI can be situated far from tissues with abundant 5-HT_{1A}R expression [36]. The cerebellar ROI was defined in 3 MRI planes where the cortex sampled was located at least twice the FWHM ventral and medial to ventral occipital cortex and posterior and medial to basal temporal cortex to avoid “spilling in” of radioactive counts from areas with abundant 5HT_{1A} receptors [36,37]. The posterior border of the cerebellar ROI also was situated >one cm from the brain edge to avoid spilling in of radioactive counts from the venous sinuses on the posterior surface of the

cerebellum (which contain a higher concentration of radioactive polar metabolites than the cerebellar cortex, which only has a 4 to 5% blood volume)[38-40]. ROI placement was limited to axial planes at or dorsal to plane 56 (of 63) to measure from planes where the signal-to-noise ratio was relatively uniform in 3D images[41].

Decay-corrected, time-radioactivity curves were obtained from the dynamic PET image for each ROI using a calibrated phantom standard to convert tomographic counts to $\mu\text{Ci/ml}$ for each time point. Regional 5-HT_{1A}R BP values were fit with a 3-parameter (simplified) reference tissue model [38,42]. The BP values obtained using this model are less variable than those obtained using compartmental modeling approaches in which the plasma [¹¹C] WAY-100635 concentration is the input function, because the rapid clearance of [¹¹C] WAY-100635 from plasma limits the accuracy of quantitating metabolites at late imaging times [38].

The mean BP values were compared between the depressed and control groups using unpaired t-tests. Because the aim was to replicate previous results, one-tailed tests were used, with p-values corrected (Bonferroni) for comparisons in two ROI. In ROI where the original results [1] were replicated by the independent data set assessed herein, the power of *post hoc* clinical correlations was enhanced by combining the depressed samples from the current study with that from the original study (n=28) to assess relationships between regional BP values and illness severity ratings and plasma cortisol levels.

Results

The demographic characteristics and mean 5-HT_{1A}R BP values of the study samples appear in table 1. Mean depression severity was in the moderately depressed range (mean HRSD₁₇=18±7.0 and HRSD₂₅ = 23±9.3) and mean STAI score was 23±10. When the MDD subjects with only MDD relatives was considered alone, their depression ratings were comparable (mean HRSD₁₇=21±4.3; mean HRSD₂₅ = 27±4.9; mean STAI=26±9.0). The mean stressed plasma cortisol concentrations trended toward being higher (0.05<p<0.1) in the depressives (13.1±7.77 $\mu\text{g/dl}$) than the controls (10.4±4.08 $\mu\text{g/dl}$). The mean time of day for assaying these levels did not differ significantly between groups.

The mean 5-HT_{1A}R BP was reduced 25.6% in the MTC (t=2.51; p<0.005) and 43.0% in the raphe (t=4.07; p<0.001) in depressives versus controls (table 1). The magnitudes of these differences were similar when the MDD cases who had only MDD first-degree relatives were considered alone, in whom the 5-HT_{1A}R BP was reduced 27.7% in the MTC (t=2.62; p=0.010) and 41.7% in the raphe (t=3.88; p<0.001) in depressives versus controls. The difference in the raphe also remained significant when considering only the small sample of BD spectrum cases alone (p<0.005).

The 5-HT_{1A}R BP values in the MTC correlated with those in the midbrain (r =0.553; p<0.01). In the combined sample of depressed patients from our current and previous studies (n=28) no relationship was evident between HRSD scores (17 item) and 5-HT_{1A}R BP values in the raphe (r = -0.27; p>0.1), but the corresponding correlation involving BP values in the MTC trended toward significance (r= -0.33; 0.1<p<.05). The anxiety ratings were not correlated with BP values in the MTC or the raphe (p>0.2). The plasma cortisol levels were not correlated with the BP values in either ROI (p>0.2).

Discussion

In this independent subject sample, the mean 5-HT_{1A}R BP was reduced 26% in the MTC (p<0.005) and 43% in the raphe (p<0.001) in depressives versus controls, replicating the findings in our original sample, which showed BP reduced 27% in MTC (p<0.025) and 42%

in the raphe ($p < 0.02$) in depressives versus controls [1]. Importantly, these differences remained significant when the MDD cases with only MDD first-degree relatives were considered alone (table 1).

These data were compatible with the results of 5-HT_{1A}R agonist challenge studies, which showed that unmedicated MDD subjects have blunted hypothermic and adrenocorticotropin (ACTH) and cortisol release relative to controls in response to ipsapirone or buspirone [43-45]. Since 5-HT_{1A}R stimulation induced hypothermia and ACTH/cortisol release are thought to distinguish pre- and postsynaptic 5-HT_{1A}R stimulation, respectively, in humans and rats, 47 these findings were compatible with the PET data implicating both pre- and postsynaptic 5-HT_{1A}R in MDD.

Moreover, the magnitudes of the differences we found in 5-HT_{1A}R BP between depressives and controls appear similar to those reported by several other neuroimaging studies. For example, relative to healthy controls the post-synaptic 5-HT_{1A}R BP values were decreased by 20 to 28% in women with *post partum* depression[46], and by 18 to 26% in depressed subjects with BD [47], and the 5-HT_{1A}R BP in the raphe was reduced 37% in elderly depressives [11]. However, other studies reported reductions that were smaller in magnitude [5] or differences that were not significant with respect to controls [13], suggesting that heterogeneity exists with respect to the presence of abnormal 5-HT_{1A}R binding in the conditions encompassed by DSM-IV criteria for MDD.

Specificity of 5-HT_{1A}R binding abnormalities in mood and anxiety disorders

The specificity of 5-HT_{1A}R binding abnormalities to mood disorders has not been entirely established. Studies in experimental animals have associated reductions in post-synaptic 5-HT_{1A}R in multiple brain regions (including the MTC) following repeated stress in rats and tree shrews (see below) and in monkeys which show depressive-like behaviors [48]. In addition, humans with chronic fatigue syndrome have been shown to have reductions in 5-HT_{1A}R binding that resemble those in MDD [49]. Nevertheless, some psychiatric disorders which are accompanied by physiological or psychological stress, such as post-traumatic stress disorder[50], schizophrenia [51], or restricting-type anorexia nervosa[52] have shown no differences in 5-HT_{1A}R binding relative to healthy controls. In addition, women recovered from bulimia-type anorexia nervosa had significantly *increased* [¹¹C]WAY-100635 binding potential in the MTC, raphe, cingulate, temporoparietal and prefrontal cortices relative to controls.[52] Furthermore, the data reviewed below on *post mortem* studies of suicide victims suggest that nonspecific depressive symptoms or stress exposure does not account for reductions in 5-HT_{1A}R binding abnormalities in mood disorders.

We assessed the specificity of 5-HT_{1A}R binding abnormalities by additional studies of depressive subtypes that were distinct from those studied either in our original and current studies, and anxiety disorders that commonly occur co-morbidly with depression. In each of these studies regional 5-HT_{1A}R distribution volumes (*DV*) were measured along with *BP* values using arterial plasma input functions corrected for plasma protein binding of the parent radiotracer to ensure that the differences found in depression were not attributable to differences in free and nonspecific radioligand binding in the reference tissue:

Post Partum Depression—The 5-HT_{1A}R binding was assessed in women who developed post partum depression (PPD) to elucidate mechanisms underlying the greater risk of MDD in women and the increased risk for MDD and BD onset in the *post partum* period. Ovarian steroids exert robust effects on 5-HT_{1A}R and 5-HT transporter (5-HTT) expression in monkeys [53]. Moses et al.[46] compared 5-HT_{1A}R BP between 9 unmedicated women with PPD (5 MDD, 4 BD) and 9 *post partum* control women using PET, [¹¹C]WAY-100635, 90-min emission scans, and arterial input functions. Age, time since delivery, and reproductive

hormones did not differ between groups. Postsynaptic 5-HT_{1A}R receptor binding in PPD was reduced 20 to 28% relative to controls, with the most significant reductions ($p < 0.001$) located in the MTC and anterior cingulate cortices.

Bipolar Disorder—To address the limitations in quantitating distribution volumes of [*carbonyl*-¹¹C]WAY100635, we used PET and the 5-HT_{1A}R selective radioligand, [¹⁸F]FCWAY, to assess the specificity of 5-HT_{1A}R binding abnormalities in BD [47]. The mean 5-HT_{1A}R BP was *decreased* in unmedicated, depressed BD subjects ($n=14$) vs HC ($n=22$) in anterior cingulate cortex (ACC; $p=0.005$), posterior cingulate cortex (PCC; $p=0.002$), left parietal cortex ($p < 0.001$), and left ($p=0.008$) and right anterior insula ($p=0.017$). In contrast, the difference between groups in the raphe did not reach significance. The differences in post-synaptic 5-HT_{1A}R BP remained significant when a range of modeling approaches and reference tissues was applied (no significant differences existed between groups in reference tissues), and were similar in magnitude to those found herein in the MTC (18% to 26%).

Panic Disorder—The 5-HT_{1A}R also has been implicated in the some pathological anxiety states, as thermic and ACTH/cortisol responses to 5-HT_{1A}R agonist administration are blunted in panic disorder as well as in MDD, and 5-HT_{1A}R “knock-out” mice manifest exaggerated anxiety responses (reviewed in [14,54]). Using PET and [¹⁸F]FCWAY we demonstrated that the mean 5-HT_{1A}R BP was decreased in unmedicated panic disorder subjects ($n=16$) relative to healthy controls ($n=16$) in ACC ($p < 0.001$), PCC ($p < 0.001$), and midbrain raphe ($p < 0.001$) [14]. These abnormalities extended both to panic disorder subjects with comorbid depression ($n=8$) *and to those without comorbid depression* ($n=8$). These abnormalities also were significant in subjects who were *naïve to psychotropic drug treatment* ($n=9$).

Temporal Lobe Epilepsy (TLE)—The risks for depression and suicide are increased in TLE compared to control groups who are healthy or who suffer from other types of epilepsy. The 5-HT_{1A}R binding in depressed TLE ($n=16$) versus TLE cases with no history of major depressive episodes ($n=21$) were compared using PET and [¹⁸F]FCWAY. The mean 5-HT_{1A}R DV (corrected for protein binding) and BP were decreased in the depressed TLE cases versus the nondepressed cases in the anterior ($p=.006$) and posterior ($p=.03$) cingulate cortices, anterior insula ($p=.009$), raphe ($p=.008$), right hippocampus ($p < .001$), right amygdala ($p=.03$), and right parahippocampal cortex ($p=.03$) [55,56].

Post-Traumatic Stress Disorder (PTSD)—The mean 5-HT_{1A}R BP and DV did not differ significantly between unmedicated subjects with PTSD ($n=12$) vs. matched, never traumatized controls in any region studied. No difference in 5-HT_{1A}R DV or BP was observed between PTSD patients with current or past diagnosis of depression versus those without depression. PTSD constitutes a particularly useful comparator condition for considering the neurobiological basis of 5-HT_{1A}R abnormalities in MDD, because most studies find no evidence for glucocorticoid hypersecretion in PTSD. [57]

Treatment Effects in MDD, BD—Alterations in 5-HT_{1A}R function (especially enhancement of post-synaptic 5-HT_{1A}R function) appear critical to the efficacy of ADT in animal models that predict antidepressant efficacy (e.g., [58]). This effect does not involve changes in 5-HT_{1A}R density, however [7,9,59]. Nevertheless, because treatment may reduce cortisol hypersecretion, we assessed effects of chronic SSRI treatment on 5-HT_{1A}R binding. The 5-HT_{1A}R BP did not significantly change between the pre- and post-treatment scans in the raphe, MTC, lateral orbital cortex, medial occipital/ posterior cingulate cortex, or parietal cortex. [6] Among the 22 subjects for whom the clinical response-to-treatment was established, the treatment non-responders ($n=7$) had higher baseline BP values in the left ($p=0.01$) and right orbital cortex ($p=0.02$) than the responders ($n=15$), implying that higher baseline 5-HT_{1A}R

binding was associated with poorer response to treatment, consistent with the previous report of Parsey et al.[60]. These data suggest the hypothesis that those patients who have reduced 5-HT_{1A}R binding are more likely to benefit from treatments that enhance 5-HT_{1A}R function/transmission.

The observation that chronic antidepressant drug treatment did not significantly change cerebral 5-HT_{1A}R binding is consistent with preclinical evidence that the alterations in serotonergic function associated with ADT are not accompanied by changes in 5-HT_{1A}R density [7,9,59,61,62]. The preclinical effects of antidepressant drugs on 5-HT_{1A}R function nevertheless suggest that these agents would compensate for a reduction in postsynaptic 5-HT_{1A}R function in primary mood disorders, even if these agents did not correct abnormal 5-HT_{1A}R binding [7,9,58]. This hypothesis is compatible with the clinical observation that major depressive episode (MDE) typically recur following the cessation of antidepressant drug treatment.

In contrast, some mood stabilizers (i.e., lithium, divalproex) increases gene expression of BAG-1, which would reduce the translocation of cortisol-GR into cell nuclei, and attenuate the effect of glucocorticoid receptor stimulation.[63] In both cross-sectional and longitudinal studies we demonstrated that mood stabilizer treatment with lithium or divalproex is associated with increased (toward normative levels) 5-HT_{1A}R binding in BD samples [64].

This increased 5-HT_{1A}R binding during mood stabilizer treatment may alternatively reflect neurotrophic/ neuroprotective effects on the neuronal processes which express 5-HT_{1A}R protein. Lithium and divalproex also robustly increase the levels of the cytoprotective protein bcl-2 in various areas of the rodent brain and in cells of human neuronal origin.[65] Bcl-2 exerts both neuroprotective and neurotrophic effects in the mammalian CNS.[65]

Finally, the elevation in 5-HT_{1A}R binding could reflect enhancement of 5-HT_{1A}R promoter activity, since high affinity AP-1 sites exist in the 5-HT_{1A}R promoter and both lithium and divalproex robustly increase AP-1 DNA binding activity [66,67]. Nevertheless, lithium does not directly increase 5-HT_{1A}R density in the cortex of experimental animals, implying the effect in BD may be specific to the pathophysiological state[68].

Interpretation of reduced 5-HT_{1A} receptor binding in mood disorders

Abnormally decreased 5-HT_{1A}R BP in FPDD/BD most likely reflects either down-regulation of receptor density or a reduction in the number of brain cells expressing 5-HT_{1A}R. In contrast, reduced [¹¹C]WAY-100635 and [¹⁸F]FCWAY binding in depression are not expected to reflect a compensatory responses to abnormal 5-HT release. The 5-HT_{1A}R density and mRNA expression appear insensitive both to reducing 5-HT transmission by lesioning the raphe or administering the 5-HT depleting agent, PCPA, and to increasing 5-HT concentrations using SSRI or monoamine oxidase inhibitors (MAOI) [61,62,69-73]. Moreover, [¹¹C]WAY-100635 and [¹⁸F]FCWAY binding appear insensitive to endogenous 5-HT concentrations, as in baboons administration of agents which increase 5-HT release, including fenfluramine, citalopram, and amphetamine, does not alter [¹¹C]WAY-100635 binding.[74] The insensitivity to endogenous 5HT is partly related to the ~50-fold greater 5-HT_{1A} receptor affinity of WAY-100635 relative to endogenous 5HT (based upon KD).

In the current study the specificity of the 5-HT_{1A}R BP measures was limited by the dependency of the modeling approach on cerebellar [¹¹C]WAY-100635 concentrations. The abnormal 5-HT_{1A}R BP values in depression thus may have been accounted for either by reduced 5-HT_{1A}R specific binding in the target ROI or by elevated cerebellar [¹¹C]WAY-100635 concentrations. However, there is no reason to expect that abnormal 5-HT_{1A}R expression exists in the cerebellum in mood disorders, and the PET studies reviewed above which involved

arterial input functions did not find differences in the radioligand distribution volume in the cerebellum.

The abnormal 5-HT_{1A}R binding in primary mood disorders is also unlikely to be accounted for by differences in nonspecific binding because of the very high selectivity of [*carbonyl*-¹¹C]WAY-100635 for 5-HT_{1A}R. WAY-100635 shows greater than 100-fold selectivity for 5-HT_{1A}R relative to a variety of other receptors, reuptake sites, and ion channels [75,76]. These data are consistent with the high specific-to-nonspecific binding ratio, the rank order of uptake across regions, and the very low binding in cerebellum in [*carbonyl*-¹¹C]WAY-100635 images.[38,77] In humans [*carbonyl*-¹¹C]WAY-100635 is almost exclusively metabolized to [¹¹C]cyclohexane-carboxylic acid and more polar radioactive metabolites[40, 77]. The only radioactive metabolite of [*carbonyl*-¹¹C]WAY-100635 in humans with high affinity for 5-HT_{1A} receptors is [*carbonyl*-¹¹C]desmethyl-WAY-100635, which Osman et al. [40] found detectable at only a “possible trace level” in plasma 60 min after injection. It is also unlikely that differences in radiolabeled metabolite concentrations contributed to the abnormal BP values in the depressives, since we showed previously that depressives metabolized [*carbonyl*-¹¹C]WAY-100635 at a similar rate as healthy controls.[1] Nevertheless, a disadvantage to [*carbonyl*-¹¹C]WAY-100635 is that its rapid clearance from plasma limits the accuracy of quantitating metabolites at late imaging times [38], so that BP values obtained using compartmental modeling approaches in which the plasma [¹¹C]WAY-100635 concentration is the input function are highly variable.

To address this limitation of [*carbonyl*-¹¹C]WAY-100635 with respect to quantitative modeling, Lang, Eckelman and colleagues[78] developed an analog of CWAY labeled with [¹⁸F] to take advantage of the longer radioisotope half-life (110 min). The compound used in these studies is the trans 4-fluorocyclohexanecarboxylic acid analog of CWAY and is referred to as FCWAY. The *in vitro* affinity of this ligand for the 5-HT_{1A} receptor is ~ 1 nM, comparable to WAY 100635. FCWAY specific binding could be blocked by co-injection of CWAY [78]. The primary metabolites are [¹⁸F]fluorocyclohexanecarboxylic acid and [¹⁸F]fluoride. As with the previous studies with [¹¹C]WAY-100635, there was evidence that the carboxylic acid crosses the blood-brain-barrier to some extent, although this contributed to no more than 7% of the signal in the cerebellum and less in other regions with specific binding. Tracer kinetic modeling analysis showed that the data were well described by a model with two tissue compartments and the total DV was a useful measure of receptor binding. Across brain regions, DV estimates for [¹⁸F]FCWAY correlated (*r*= 0.99) with those measured from [¹¹C]CWAY, excepting brain tissues located near the skull (the [¹⁸F]fluoride secondary metabolite of FCWAY binds to bone, confounding measures near skull).

Correlation with *in vitro* studies of depression conducted *post mortem* or *antemortem*

The sensitivity and specificity for measuring 5-HT_{1A}R binding using neuroimaging are limited by the low spatial resolution of PET. For example, the 5-HT_{1A}R specific binding measured over the raphe appears lower than expected based upon *post mortem* autoradiographic data [36], since the small size of the raphe relative to the spatial resolution of PET results in extensive partial volume effects[37]. Moreover, while extant PET radioligands measure binding to an 5-HT_{1A}R antagonist, many *post mortem* studies assessed binding to the 5-HT_{1A}R agonist, [³H] 8-OH-DPAT. In healthy humans, 5-HT_{1A}R B_{max} measured using [³H]WAY-100635 correlate tightly with those measured using [³H]8-OH-DPAT, with B_{max} measured using [³H]WAY-100635 being 60 to 70% higher in most regions than when measured using [³H]8-OH-DPAT[79]. Thus, the results of *post mortem* and *antemortem* studies of brain tissue obtained from individuals with primary mood disorders provides important confirmatory and, in some cases, complementary information regarding the nature of 5-HT_{1A}R abnormalities in depression.

In Vitro Studies of 5-HT_{1A}R Density in Primary Mood Disorders—In the hippocampus and neocortex, *post mortem* studies of primary MDD have reported abnormal reductions of post-synaptic 5-HT_{1A}R density and mRNA expression, although these studies have the limitation of having even smaller sample sizes than those of neuroimaging studies. The 5-HT_{1A}R mRNA levels have been shown to be significantly reduced in the hippocampus [2,80] and the dorsolateral PFC [80] in MDD subjects *post mortem*. Bowen et al. [10] found reduced [³H]8-OH-DPAT binding in the temporal polar and lateral orbital cortices in 7 elderly subjects (6 MDD, 1 BD) who died of natural causes. Bowen et al [10] found the reduction in 5-HT_{1A}R in two regions was associated with a reduction in “grey matter wet weight”, which was decreased 29% in the pars opercularis (ventrolateral PFC) and 38% in temporal polar C. In the entire pars opercularis and temporal polar C the magnitude of the significant reduction in 5-HT_{1A}R B_{max} (45% and 59%, respectively; $p < 0.05$) was greater than the reduction in grey matter weight (29% and 38%, respectively) in depressives versus controls, and the 5-HT_{1A}R density was also reduced in these regions (24% in both regions) when measured per unit of grey matter tissue. Finally, Francis et al.[81] reported that 5-HT_{1A}R density measured *antemortem* by [³H]8-OH-DPAT binding was decreased 29% ($p < 0.01$) in superficial layers of the dorsal anterolateral PFC tissue (BA 9) removed during neurosurgical intervention for intractable depression in 4 subjects with primary MDD or BD relative to neurosurgical controls.

In the raphe, the *post mortem* literature suggests a more complex pattern of 5-HT_{1A}R binding abnormalities exists in depression. In suicide victims who were both depressed prior to suicide and had no history of alcoholism, Arango et al.[3] observed a significant, 38% reduction of the 5-HT_{1A}R binding capacity (reflecting a reduction of both 5-HT_{1A}R density and of the total area of the DRN labeled by [3H]OH-DPAT) relative to controls. This finding was consistent with the 37 to 43% reductions in 5-HT_{1A}R binding we (table 1; also [1]) and others[11] found in the raphe in primary depressives using PET. However, in the dorsal and ventrolateral subnuclei of the dorsal raphe nucleus the 5-HT_{1A}R binding was abnormally *increased* in depressed in another study of depressed suicide victims relative to controls[4].

In contrast to the agreement between the results of most *post mortem* studies, PET imaging studies and 5-HT_{1A}R agonist challenge studies regarding the status of *post-synaptic* 5-HT_{1A}R binding in primary MDD, the results of *post mortem* studies of 5-HT_{1A}R binding in *unselected* suicide victims vary widely (reviewed in[1]). The highly variable results across suicide studies suggest that the nonspecific presence of depressive symptoms or suicidal behavior provides neither sensitivity nor specificity for identifying subjects with abnormal 5-HT_{1A}R binding. Suicidal behavior and depressive symptoms are nonspecific clinical signs/symptoms occurring in a variety of medical and psychiatric conditions. Only 1/3 to 1/2 of suicides appear to have suffered from a MDE prior to death and many depressed suicides have MDE arising secondary to other psychiatric or medical conditions[30,82]. The “primary” versus “secondary” affective disease distinction thus may relate to the sensitivity for identifying 5-HT_{1A}R abnormalities in depression, since nearly all studies of primary mood disorders found reduced post-synaptic 5-HT_{1A}R mRNA expression, binding or sensitivity.

Neurobiological Significance of Decreased 5-HT_{1A}R Binding in Depression

In humans the 5-HT_{1A}R is expressed presynaptically on 5-HT cell bodies in the raphe (as a somatodendritic autoreceptor) and postsynaptically in other brain regions [83]. In humans and monkeys, the density of 5-HT_{1A}R is very high in the raphe and parts of the hippocampal formation, high in hypothalamus, insula, temporal, cingulate and ventral prefrontal cortices, moderately high in occipital and parietal cortices, and very low in cerebellum, striatum, thalamus and white matter.[84,85] In the raphe stimulation of presynaptic 5-HT_{1A} autoreceptors reduces 5-HT release by inhibiting 5-HT neuronal firing, and reduces 5-HT

synthesis by inhibiting tryptophan hydroxylase.[73,86] Alterations in 5-HT_{1A}R density in the raphe could thus influence the amount or timing of serotonin release in widespread brain areas.

In the cortex, hippocampus and amygdala postsynaptic 5-HT_{1A}R are located on pyramidal cells and interneurons, and stimulation of these receptors generally inhibits glutamate-mediated depolarization of parent neuron[59,86]. Altered 5-HT_{1A}R function exerts a major influence on neuronal activity in the amygdala and hippocampus [87-89]. Reduced 5-HT_{1A}R function in the amygdala is hypothesized to play a role in disinhibiting amygdala responses to emotional stimuli [89], potentially contributing to the pathological emotional behavior associated with mood disorders [87,90]. In addition, stimulation of 5-HT_{1A}R in the PFC plays a major role in modulating 5-HT release during stress,[91] so reduced 5-HT_{1A}R binding in this cortex may alter the amount of 5-HT release during stress.

Postsynaptic 5-HT_{1A}R also are expressed abundantly by astrocytes and some other glia [83, 92,93]. Stimulation of astrocyte-based 5-HT_{1A}R causes astrocytes to acquire a more mature morphology and to release the trophic factor, S-100B, which promotes growth and arborization of serotonergic axons.[94] S-100B is primarily released by astroglia in the developing brain, when it plays a role in the development of the serotonergic system[83,95]. In the adult brain S-100B plays major roles in the plasticity of 5-HT neurons[96]. The importance of 5-HT_{1A}R function on 5-HT system development is evident in 5-HT_{1A}R knockout mice, which showed elevated anxiety behaviors specifically as a result of deficient 5-HT_{1A}R function during development.[97]

S-100B also plays a role in maintaining the cytoskeleton in adult animals by promoting tubulin polymerization and inhibiting PKC-mediated breakdown of microtubules.[98] In addition, stimulation of neuron-based 5-HT_{1A}R inhibits PKA-mediated disassociation of the proteins comprising the tubulin polymers of the cytoskeleton. Administration of 5-HT_{1A}R antagonists, antibodies to S-100B, or agents that deplete 5-HT all produce similar losses of dendrites, spines and/or synapses in adult and developing animals, effects which are blocked by administration of 5-HT_{1A}R agonists or SSRIs.[98] The role of postsynaptic 5-HT_{1A}R function in maintenance of the cytoskeleton has led to the hypothesis that a reduction of 5-HT_{1A}R function may comprise a risk factor for developing the neuropathological abnormalities identified in limbic and paralimbic cortical areas in mood disorders (reduced cortex volume, reduced synaptic proteins, increased neuronal density, reduced glial counts) [99,100].

Regulation of 5-HT_{1A} Receptor Expression by Glucocorticoid Hormones—

Although 5-HT_{1A}R density and mRNA expression is relatively insensitive to reductions in 5-HT transmission associated with raphe lesions or serotonin depletion[59,69-71], or to elevations of 5-HT transmission resulting from SSRI or MAOI[59,61,62,72], the 5-HT_{1A}R expression is potently inhibited by adrenal corticosteroids. Postsynaptic 5-HT_{1A}R gene expression is under tonic inhibition by adrenal steroids in the hippocampus and some other regions. Thus, in rodents the hippocampal 5-HT_{1A}R mRNA expression is increased by adrenalectomy and decreased by corticosterone (CORT) administration or chronic stress.[2, 18,19,22,101,102]. The stress-induced down-regulation of 5-HT_{1A}R expression is prevented by adrenalectomy. Mineralocorticoid receptor stimulation has the most potent effect on down-regulating 5-HT_{1A}R, although glucocorticoid receptor stimulation also contributes to this effect [17,18,103].

Thus one factor which may contribute to the reduction in 5-HT_{1A}R binding in depression is increased cortisol secretion associated with primary mood disorders[2]. The magnitude of the reduction in 5-HT_{1A}R density and mRNA levels induced by stress-induced glucocorticoid secretion in rodents is similar to that of the differences between depressed and healthy humans. For example, in tree shrews chronic social subordination stress decreased the density of 5-

HT_{1A}R in the posterior cingulate, parietal cortex, prefrontal cortex, and hippocampus (by 11% to 34%),[22] similar to the magnitude of reduced 5-HT_{1A}R BP found by Sargent et al.[5] and Drevets et al.[1] in these regions. Thus, elevated cortisol concentrations may conceivably induce a relatively widespread reduction of 5-HT_{1A}R expression.

Relative to healthy controls, depressives show elevated levels of cortisol in plasma, hypertrophy of the adrenal and pituitary glands, and exaggerated cortisol response to ACTH stimulation (presumably reflecting adrenal hypertrophy)[26,104,105]. The relationship between 5-HT_{1A}R binding in depression and current measures of cortisol secretion may prove complex, however. Because 5-HT_{1A}R stimulation increases plasma ACTH and cortisol secretion, down-regulation of 5-HT_{1A}R gene expression is thought to comprise a compensatory mechanism for inhibiting cortisol release[43,106]. To the extent that this response maintains cortisol levels near the normative range, peripheral endocrine measures may no longer reflect the history of excessive cortisol secretion and reduced 5-HT_{1A}R BP may instead reflect the recent propensity to hypersecrete cortisol in depression. This interaction may explain the lack of correlation between hippocampal 5-HT_{1A}R BP and current cortisol concentrations in our current and previous studies [1]. Assessments of the pathophysiological diathesis to hypersecrete cortisol may, therefore, provide more sensitive correlates of reduced 5-HT_{1A}R binding. It thus is noteworthy that our previous study[1] found reduced 5-HT_{1A}R BP in a depressed sample who showed significantly elevated stressed plasma cortisol levels[1], and that in the current study we also found reduced 5-HT_{1A}R BP in an independent depressed sample whose stressed plasma cortisol levels trended toward being elevated with respect to controls (0.05<p<0.10; the mean values in our original sample of 12.5±2.8 and 9.7±2.1 µg/dl, in depressives and controls, respectively, were similar to those obtained in the current sample of 13.1±7.8 and 10.4±4.1 in depressives and controls, respectively).

Two PET studies attempted to assess the effect of glucocorticoid hormone on 5-HT_{1A}R using PET and [¹¹C]WAY-100635. The first showed no change in 5-HT_{1A}R BP at 12 hours after infusion of hydrocortisone 100 mg [107]. However, while mRNA expression decreases within hours, the reduction in 5-HT_{1A}R protein is not evident until 2 to 4 days later [2]. The other study showed no reduction in 5-HT_{1A}R BP in patients with medical disorders for which they received prednisolone >7.5 mg [108]. However, prednisolone predominantly stimulates glucocorticoid receptors and has relatively low affinity for mineralocorticoid receptors, and it is the latter steroid receptor subtype that exerts the most prominent effect on 5-HT_{1A}R[17] mRNA expression. Thus the design of these studies may have reduced the sensitivity for detecting glucocorticoid-mediated effects on 5-HT_{1A}R binding.

Genetic Correlations—Finally, the amount of variability of 5-HT_{1A}R binding that is modulated by gene polymorphisms associated with the vulnerability to depression remains unclear. A functional polymorphism in the 5-HT_{1A}R promoter region was associated with increased risk for MDD and suicide.[109] The allele associated with MDD leads to decreased activity by the repressor protein NUDR, which may in turn lead to increased 5-HT_{1A}R expression in the raphe. In contrast, the NUDR repressor may exert opposite effects on hippocampal and cortical postsynaptic 5-HT_{1A}R, as decreased NUDR function reduced the expression of postsynaptic 5-HT_{1A}R in vitro[109]. One PET study of 5-HT_{1A}R BP in depressed subjects reported that the G-allele of this 5-HT_{1A}R promoter polymorphism was associated with higher 5-HT_{1A}R binding[13], although this relationship was not replicated by another group [110]. The latter group also assessed the relationship of the common variable number tandem repeat polymorphism [short (S) and long (L) alleles] of the 5-HT transporter gene to 5-HT_{1A}R BP, and found that binding was lower in all brain regions in subjects with short (SS or SL) genotypes than in those with long (LL) genotypes. The short genotype has been associated with an increased vulnerability for developing depression within the context of stress [111], suggesting the hypothesis that this increased risk for depression is mediated by a

heritable diathesis to more profoundly down-regulate 5-HT_{1A}R expression in response to stress.

Summary

It remains unclear whether the reduction in 5-HT_{1A}R function and expression in mood disorders constitutes a neurodevelopmental or an acquired abnormality. This issue is of interest because interruption of 5-HT_{1A}R function during neurodevelopment persistently alters the function of emotion modulating systems [97]. Nevertheless, the reduction in 5-HT_{1A}R binding and mRNA expression in depression may arise secondarily to cortisol hypersecretion, as the 5-HT_{1A}R mRNA expression and density are under tonic inhibition by glucocorticoid receptor (GR) stimulation[2]. Moreover, the mood and anxiety disordered subgroups with reduced 5-HT_{1A}R binding may be limited to those with a diathesis to hypersecrete cortisol (e.g., [1,2].

Although antidepressant drug treatment does not normalize the abnormalities in 5-HT_{1A}R in depression [5,6], evidence from preclinical studies suggests that chronic administration of these agents results in enhancement of 5-HT_{1A}R function[7,9]. Potentially consistent with this evidence, treatment responders have lower 5-HT_{1A}R binding than nonresponders[6,60], suggesting the hypothesis that those patients who have reduced 5-HT_{1A}R binding are more likely to benefit from treatments that enhance 5-HT_{1A}R function/ transmission.

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Figure 1.

Co-registered PET and MRI sections through the mesiotemporal cortex and midbrain. This region included areas of high 5HT_{1A}R density (hippocampus) along with areas of moderate density (amygdala, periamygdaloid cortex). By including amygdala (Am) and hippocampus (Hi) together, errors in distinguishing these two structures are avoided. The raphe (Ra) ROI was defined on the PET, but in the co-registered MRI it is evident that this circular ROI overlies the midbrain area where the dorsal and median raphe nuclei are known to be situated. Reproduced from [1].

Figure 2.
Regional 5HT_{1A}R binding for the combined samples from our current and previous[1] studies of recurrent depression.

Table 1

Demographic and clinical characteristics and regional binding potentials for [^{11}C]WAY-100635 of the study samples.

Parameter	Control	Depressed	MDD (with MDD relatives)	BD Spectrum
Sample size (n)	8	16	11	5
Mean Age (SD)	32.4 (12.1)	32.4 (10.0)	30.8 (7.8)	35.8 (14.1)
% female	50	63	55	80
Mean (SD) BP: MTC	9.17 (2.51)	6.82 (1.20) ^a	6.63 (1.29) ^b	7.26 (0.94) ^c
Mean (SD) BP: raphe	4.56 (1.26)	2.60 (0.65) ^a	2.66 (0.68) ^a	2.47 (0.64) ^a

^a $p < 0.005$, relative to controls

^b $p = 0.01$, relative to controls

^c $0.05 < p < 0.10$, relative to controls

Abbreviations: BD – bipolar disorder; BP – binding potential; MDD- major depressive disorder; MTC – mesiotemporal cortex

Table 2
Specificity of 5-HT_{1A}R Imaging abnormalities in mood disorders

Post-synaptic 5-HT_{1A} R decreased in

- MDD (depressed, remitted)
- Bipolar disorder (depressed)
- Panic Disorder with and without comorbid MDD
- Depressed TLE vs. nondepressed TLE
- *Post partum* depressed vs *post partum* control
- Chronic Fatigue Syndrome

5HT_{1A}R not different or increased in

- PTSD
 - Schizophrenia
 - Anorexia nervosa
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See text for references